To sleep or not to sleep

Gazendam, Joost Alexander Christiaan

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New insights in sleep-wake cycles and circadian rhythmicity in the Intensive Care Unit

J.A.C.Gazendam

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Hoewel het behouden van een normale slaap-waak en circadiane ritmiek een belangrijke fysiologische en psychologisch behoefte is, blijkt dit lastig te realiseren in de high-tech omgeving van de Intensive Care Unit (ICU). Het totale aantal uren dat patiënten op deze afdeling slapen is niet per definitie afwijkend, maar wel de verdeling en de fragmentatie ervan. Bijna de helft van het aantal uren slaap vindt plaats gedurende de dag, waarbij zowel overdag als 's nachts geluidsoverlast in minder dan 20% van de gevallen de oorzaak is van de slaapverstoringen. Ziekere patiënten lijken een sterkere verschuiving van hun circadiane ritmiek te vertonen, hoewel geen enkele patiënt volledig ritmeloos blijkt te zijn. Naast de geluidsoverlast is het sterk afwijkende licht-donker ritme op de ICU een belangrijke omgevingsfactor die medeverantwoordelijk zou kunnen zijn voor deze circadiane ritmeveranderingen. De lichtintensiteit is op deze afdeling overdag lager, en 's nachts hoger, in vergelijking met een controle groep. Daarnaast is het verschil in intensiteit tussen licht en donker ook significant lager. De aanwezigheid van ramen op de kamer geeft geen garantie van een natuurlijk licht-donker dag-nacht ritme. Nachtelijke sedatie met als doel het slaap-waak en circadiane ritme te herstellen leidt niet tot een reductie in het aantal geslapen uren gedurende de dag. Herstel door middel van het aanbieden van tijdstipaanduidende factoren (televisie-uitzendingen, 24-uur klokken) hebben potentieel een sterker effect. Een normaal slaap-waak ritme en circadiane ritmiek zou in plaats van een luxe een van de prioriteiten moeten zijn op de ICU.

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Postulates

1. Sleep in the ICU should be considered a medical priority rather than a luxury.

2. Continuous EEG recording may be a valid, non-invasive marker for early sepsis.

3. Absence of rhythm may be fatal.

4. ICU patients may display a better sense of rhythm in bed than on the dance floor.

5. A windowed ICU room does not guarantee a normal dark/light rhythm.

6. Overnight sedation mimics a behavioral state of sleep, not necessarily a physiological one.

7. The BBC can inform both mind and body.

8. 42.19% of statistics are made up on the spot.

9. A high IQ and strong common sense are only weakly correlated.

10. In both a surgical residency program and a marathon, the last 0.2-mile is where it counts.

11. If academia pays peanuts, don't be surprised if it attracts monkeys.

12. A biker knows why a dog sticks its head out of the car window.

13. When you are riding lead, don't spit.

14. It may be better to be scared to death than bored to death.

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in the Intensive Care Unit

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Chapter 1

An Introduction to Sleep in the Intensive Care Unit

INTRODUCTION

Sleep is an essential physiological need, but can be difficult to achieve in the high-tech environment of the modern intensive care unit (ICU). Sleep deprivation has been associated with altered respiratory-function, immune-function, neuro-endocrine control, and could be the leading cause of a phenomenon called the "ICU-syndrome". It is generally believed that the ICU environment is responsible for these sleep disruptions [1-6], with noise being considered the most disruptive of all environmental stimuli [4;7-12]}. Unfortunately, these assumptions are based on evaluations of only small populations (n=12 in largest study) of selective groups of post-operative and cardiac ICU patients. The goal of this paper is to review current literature regarding sleep in the ICU, the influence of the ICU environment on sleep and the consequences of disturbed sleep in ICU patients.

NORMAL SLEEP

Sleep can be divided in NREM or non-rapid eye movement sleep (slow wave sleep) and rapid eye movement sleep or REM sleep (active sleep) [9]. Each of these sleep states has its own set of physiological, biological, behavioral and electroencephalgraphical (EEG) hallmarks and can be demonstrated in virtually all mammals and birds [13]. The initiation of sleep occurs through NREM sleep. Using EEG criteria, NREM sleep itself can be subdivided into four distinct stages [10;13]. Each successive stage of NREM sleep represents a deeper sleep stage with the arousal threshold being lowest in stage I, and highest in stage IV (Delta sleep). Although variability exists, adults will pass consecutively through stages 1, 2, and 3, entering stage 4 about 35 minutes after sleep onset. NREM sleep comprises approximately 75% of total sleep time on a normal night.

REM and NREM sleep cycles alternate throughout the night. During REM sleep, increased central nervous system metabolic activity can be demonstrated, expressed for instance by the occurrence of dreaming in this sleep stage. Furthermore, REM sleep is characterized by muscle atonia, episodic rapid eye movements and EEG patterns (low-amplitude fast waves) analogous to wakefulness. Increased central neuronal activity occurs during the rapid eye movements. It is as if the brain is awake and active while the body is asleep. However, the increased central neuronal activity does not generally result in peripheral movements, since muscle atonia is present during REM sleep secondary to active suppression of motor-neuron activity; occasionally periodic ("phasic") twitching of the extremities may occur in this sleep stage. During an 8 hour night, REM sleep usually occurs in 4-6 separate episodes and comprises approximately 25% of total sleep

THE FUNCTION OF SLEEP

Throughout time, sleep has been considered medicinal, although it has never been scientifically proven [14;15]. Several studies have shown sleep deprivation to

contribute to the altered respiratory and immunological status in both animal and clinical studies. It is clear that more research will be required to determine the relationship between infectious diseases and sleep as currently available data is limited and mostly acquired through animal studies. However, several interesting observations from these studies should be mentioned and could give direction in future research.

The effect of sleep (deprivation) on the immune system is still largely unknown. Early studies found a slight decrease in cellular-mediated immunity resulting from sleep deprivation [16;17] as well as suppressed anti-body responses [18]. Studies by Krueger et al. (1990) and Toth et al. (1988) have demonstrated significant sleep alterations due to bacterial infections in an animal model [15;19]. EEG evaluations showed prolonged periods of NREM sleep and decreased periods of REM sleep. Also, these investigators showed increased NREM sleep to be associated with increased mortality and morbidity, if infected with S. Aureus.

A more recent study showed a direct relationship between sleep deprivation and immunological changes in humans [20]. This study involved 20 healthy volunteers who where sleep deprived for 64 hours, during which several immunological parameters were monitored. This data clearly shows an increase in circulating granulocytes and macrophages, as well as an increase in natural killer cell activity at the peak of sleep deprivation. These immunological responses disappeared after 2 nights of recovery sleep. These results suggest that sleep deprivation activates the human immune system. These statements are highly speculative and, therefore, require more thorough investigations.

Studies in normal subjects have demonstrated that short-term (24-hour) total sleep deprivation can adversely affect the respiratory system. Sleep deprivation in normal adults has been shown to decrease: forced vital capacity (FVC), maximum voluntary ventilation (MVV), hypercapnic ventilatory response by 20-40%, hypoxic ventilatory response by 29% and inspiratory muscle endurance by 24% [21-23]. These data suggest that respiratory chemosensitivity is decreased in sleep deprived patients, which could possibly lead to hypoventilation. Whether ICU patients show clinically relevant respiratory changes due to sleep deprivations requires future investigations. This could be an important issue, as many ICU patients have a compromised respiratory status or are even mechanically ventilated, and could, therefore, directly benefit from sleep promoting measures (if a positive relationship with the patients respiratory status is established).

THE INTENSIVE CARE UNIT SYNDROME

Several studies have suggested that there is an association between sleep deprivation and a phenomenon called "The Intensive Care Unit Syndrome (ICU syndrome)" [11;24-28]. This syndrome has been defined as a reversible confusional state, secondary to admission to the ICU. The ICU syndrome usually develops between the third and seventh day after ICU admission and usually resolves itself within 48 hours after discharge from the ICU. The prevalence of this

disorder is unknown, but has been estimated to occur in 12 – 38% of patients admitted to the ICU [24]. It has been more frequently reported in surgical than medical ICUs [24]. The clinical manifestations include a wide spectrum of psychological reactions including hallucinations, disorientations, anxiety, depression, delirium and fear [27;28]. The ICU syndrome has been hypothesized to have a negative influence on patient recovery by adding additional stress to the patient, who already has an impaired psychological and physical status, therefore resulting in an increased length of stay in the ICU[28].

A number of factors, including the severity of illness, the patients age, the type of surgical procedure and different medications, have all been reported to contribute to the ICU syndrome [11;24-28]. However, most investigators agree on the fact that sleep deprivation is the primary cause of this syndrome. This belief has been strengthened by sleep deprivations studies, as experimental sleep deprivation in normal subjects can reproduce the same mental status changes observed in the ICU syndrome[28;29]. Sleep-deprived healthy subjects developed slurred speech, irritability and disorientation after 2 to 5 days without sleep. Hallucinations and paranoia developed after further sleep deprivation. The signs of psychosis resolved if these sleep-deprived subjects were allowed one night of normal sleep. Analogously, the symptoms of the ICU syndrome disappear when the patients are transferred out of the ICU [28]. Helton et al. (1980), in a study correlating sleep deprivation with the ICU syndrome, demonstrated that 10% of patients with moderate sleep deprivation and 33% of patients with severe sleep deprivation developed mental status changes [28].

Treatment of the ICU syndrome should be initiated by non-pharmacological means, if possible. Means of maintaining orientation and communication are very important in treating the patient with this syndrome. It has been demonstrated that delirium is twice in common in ICUs without windows [16;30]. Therefore, daylight orientation and the placement of calendars and 24-hour clocks in the patient's room are important therapeutic measures. Benzodiazepines or haloperidol can be administered in case these non-pharmacological measures do not succeed in preventing or treating this syndrome. Sleep should be considered a priority, not a luxury, as sleep deprivation can contribute to the ICU syndrome and, therefore, affect the patient's recovery.

METHODS OF SLEEP RESEARCH

Sleep research in the ICU can be performed using objective or subjective measures. Subjective measures include questionnaires, interviews, daily sleep charting and nursing assessments [31;32]. Examples of objective measures include polysomnography and wrist actigraphy [33-37]. The subjective measurements are inexpensive and can be good forms of assessment. Questionnaires and interviews may be unreliable as many ICU patients are mechanically ventilated and sedated, but a comparison between nursing observations and polysomnography demonstrated that nurses correctly assessed sleep and wakefulness in critically ill patients 82% of the time [32]. However, other

studies have not demonstrated such a high correlation between nursing assessment and sleep [1]. Given the multitude of variables that affect patients in the ICU, objective sleep measures have been shown to be superior to the subjective measures [1].

The golden standard for determining sleep onset and duration, and the different stages of sleep, remains polysomnography [31;33]. Polysomnography systems are capable of accurately determining sleep versus wakefulness. Polysomnography generates information about electro-encephalograms (EEG), electro-oculograms (EOG), and electro-myograms (EMG). The EOG and EMG are used in distinguishing REM from non-REM sleep. Unfortunately, polysomnography is an expensive and time-consuming measure. A far simpler instrument that could be used to objectively measure sleep is the wrist-actigraph [34;38], although no ICU sleep-research data using this device is available to the present day. An actigraph is a small device worn like a wrist watch which contains a motion detector and a memory storage device. Actigraphy can indirectly quantify the sleep-wake pattern by registering movement over a 24-hour period. Actigraphy correlates strongly with polysomnography during deep sleep stages and full wakefulness, but correlations between actigraphy and polysomnography during the transitions between sleep and wakefulness and vise versa are not very strong [34;38]. Future research will have to determine whether this device has a place in ICU sleep-research.

PRESENT VIEW ON SLEEP (DEPRIVATION) IN THE ICU

Altered sleep-wake patterns, sleep deprivation and fragmentation all have been demonstrated through several polysomnographic studies of cardiac and surgical ICU patients (table I) [1-6].

Overall changes in sleep-wake patterns
- Prolonged latencies in sleep onset
- Decreased sleep efficiency
- Frequent arousals resulting in sleep fragmentation
- Increased nr. of arousals resulting in wakefullness

Changes in NREM sleep
- Increased total duration of stage 1-2 sleep
- Decreased total duration of stage 3 – 4 sleep

Changes in REM sleep
- Prolonged REM latencies
- Decreased total duration of REM sleep
- Shortened duration of each REM period

Table I: altered sleep-wake patterns in the ICU

Repeated arousals in ICU patients, regardless of its origin (noise or patient-related, like the severity of illness), disrupt the continuity of sleep during the night time hours. Patients experience interrupted sleep periods and seem to have a different distribution of sleep stages. Sleep disruptions occur in ICU patients on average every 20 minutes throughout the 24-hour period [1;2;4]. Consequently, ICU patients have difficulty attaining the deepest stages of sleep. In order to compensate for these sleep disturbances during the night, ICU patients often sleep during the day [1;2;4]. It has been demonstrated that only 50-60% of sleep in ICU patients occurs during the nighttime hours [1;2;4]. However, even if ICU patients sleep during the day, they are unable to achieve delta or REM sleep, because of reoccurring arousals. The present polysomnography studies evaluated only small populations (max. n=12) of patients with selected pathology (cardiac or post-surgery) and patients were monitored only during the nighttime hours. Future research should evaluate 24-hour periods of larger, mixed populations to confirm the present data.

The etiologies of these sleep disruptions are believed to be multi-factorial - patient, environment, and care related – although this has never rigorously been proven using continuous polysomnography [7;8;10;12;23;28;39-42] (see table II).

- Patient Factors
  - Severity of illness
  - Medication
    - REM suppressant drugs
      - Narcotics
      - Barbiturates
      - Antidepressants
    - NREM suppressant drugs
  - Pain
  - Fever
  - Loss of control (restraints, pharmacologic paralysis)
  - Fear, anxiety, psychological stress
- Physician/Nursing factor
  - Diagnostic testing
  - Nursing interventions
  - Invasive procedures
- Environmental factors
  - Lighting
  - Noise
    - Mechanical devices (alarms, ventilator, (45-76dB)
    - Backround noise (55-72dB)
    - Nursing or respiratory care (55-83dB)
    - Staff conversations (60-74dB)
  - Noxious Odors

Table II: sleep disturbing factors

Environmental stimuli has been found to be the most sleep disruptive factor in the ICU [4;7;8;11;12;43]}. The ICU is an environment of constant lighting, making it difficult to achieve sleep. Also, noxious odors have been reported to contribute to sleep disturbances in the ICU setting [7;43]. According to present data, the environmental stimulus most likely to disturb sleep in the ICU is noise [4;7;8;11;12]. The mean noise level over a 24-hour period recorded in an acute care unit was 58 dB, ranging from 50 to 76 dB [8]. The mean noise level recorded at the head of the bed was 66 dB, which is the average noise level in a busy office [8]. Recordings in the recovery room showed the following mean noise levels: 1) 59 decibels for the 7a – 3p shift; 2) 58 decibels for the 3p – 11p shift; 3) 55 decibels for the 11p – 7a shift[8]. Noise levels did not significantly decrease during the nighttime hours. In order for a patient to fall asleep, noise levels of less than 35 – 40 decibels are required. Excessive noise not only makes it difficult to fall asleep, but also causes arousals once sleep is finally achieved. There is no polysomnographic data currently available on the relationship between mechanical ventilation and sleep disruptions. However, decibel levels ranging from 60 – 65 have been measured for ventilators at the head of the bed [7;10]. Decibel levels for ventilator and infusion-pump alarms measured 20 feet away have ranged from 71- 76 decibels [7;10]. It could be hypothesized that the loud noise levels associated with mechanical ventilation and alarm systems causes sleep disruptions. However, controlled polysomnographic studies are required to determine the extent of sleep disruptions secondary to mechanical ventilation.

Beside mechanical equipment, other common sources of noise in the ICU include ambient noise (telephones, beepers, and televisions), sounds related to nursing or respiratory care (suctioning, chest physical therapy) and staff communication. In several studies, staff communication was singled out as the most disruptive noise in the ICU [4;7;40]. These investigators speculated that sounds with meaning (i.e., voices) may be more disruptive to patient than mechanical sounds without meaning. Additionally, ocean sounds and white noise have been shown to improve sleep patterns in hospitalized patients [12].

SLEEP PROMOTING MEASURES

Effective means of enhancing the quality of sleep in the ICU need to be developed. Many interventions have been suggested to improve sleep in the ICU, although data demonstrating actual sleep improvement due to these specific interventions is lacking.

However, certain common sense recommendations can be made:

- Acoustic modifications should be made to the structure of the ICU in order to reduce excessive noise levels. Each ICU room should be private, with its own doors, with a lighting system with dimmers, and, if possible, with a window to maximize natural lighting.

- Conversations in close proximity to the patient's room should be minimized, especially during the nighttime hours.
- Bedside equipment, such as IV infusion pumps and ventilators, should not be placed at the head of the bed. Also, ventilator and infusion-pump alarms should be wired outside the room. It is important that hospital staff be aware of the alarm, which can be achieved without disturbing the patient.
- White noise or ocean sounds should be considered in the ICU to foster sleep.
- The routine practices of checking vital signs throughout the night, and performing early morning x-rays and phlebotomies should be tailored to the sleep-wake cycle of patients, if their medical conditions allows this.
- Diagnostic procedures and nursing interventions should be planned to maximize uninterrupted sleep time.
- Periodic measurements of noise levels in the ICU should be taken as a quality control measure.
- Thorough sleep history should be obtained in order to identify patients with sleep disorders prior to their admission to the ICU (e.g., sleep apnea).
- Patients should be asked to fill in questionnaires after discharge, inquiring about the sleep disruptive factors they experienced and their perceived sleep quality in the ICU.

These measures are not extreme and are fairly easy to accommodate (except maybe changes in the ICU structure). Most importantly, however, is that in order to implement these initiatives, physicians and nurses need to be made aware of the specific factors causing sleep disturbances in their own ICU and develop a coordinated plan to reduce sleep disruptions secondary to these factors.

CONCLUSION

It is hard to acquire normal sleep in the ICU. Sleep disruptions, deprivation and fragmentation may have serious consequences with respect to the patient's psychological and physical functioning. The cause of the ICU syndrome may be found in sleep deprivation, as well as in decreased respiratory chemosensitivity leading to hypoventilation. Although the cause of these sleep-wake abnormalities is believed to be multi-factorial, environmental stimuli have been reported to be the most sleep disruptive of all. ICUs have been reported to be noisy around the clock. Non-pharmacological measures, which are relatively easy to achieve, should be attempted to improve sleep-wake quality before resorting to the use of sedatives. Future research should be performed in larger groups, using the golden standard of polysomnography, in order to validate many of the assumptions made by previous investigators. But above all, sleep should be considered one of the medical priorities rather than a luxury.

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Chapter 2

Abnormal Sleep/Wake Cycles and the Effect of Environmental Noise on Sleep Disruption in the Intensive Care Unit

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Little is known about sleep/wake abnormalities in intensive care and less is known about the mechanisms responsible for these abnormalities. We studied 22 (20 mechanically ventilated) medical intensive care unit (ICU) patients with continuous polysomnography (PSG) and environmental noise measurements for 24-48 hours to characterize sleep-wake patterns and objectively determine the effect of environmental noise on sleep disruption. All 22 patients demonstrated sleep/wake cycle abnormalities. There were large variations in total sleep time (TST) with the mean total sleep time per 24 hour study period of 8.8 ± 5.0 hours. Sleep/wake cycles were fragmented and non-consolidated with a mean of 57% ± 18% and 43% ± 18% of the TST occurring during the day and night, respectively. Environmental noise was responsible for 11.5% and 17% of the overall arousals and awakenings from sleep, respectively. The mean noise arousal index was 1.9 ± 2.1 arousals/hour sleep. Conclusions: 1) ICU patients are qualitatively, but not necessarily quantitatively, sleep deprived; and 2) although environmental noise is in part responsible for sleep/wake abnormalities, it is not responsible for the majority of the sleep fragmentation and may therefore not be as disruptive to sleep as the previous literature suggests.

Although previous investigators evaluating sleep patterns in ICU patients have demonstrated altered sleep architecture and sleep deprivation (1-4), little is actually known about sleep in the critically ill. Most of our current knowledge is based on studies evaluating only nocturnal sleep, rather than over 24 hour periods (1,2). Two studies have monitored polysomnography continuously for ≥ 24-hours, albeit in only a total of 19 ICU patients (3,4). Hilton (4) demonstrated a mean total sleep time per 24 hour period of 5.5 ± 3.4 hours (range 0.1-13.3) in 10 ventilated patients with respiratory insufficiency. Aurell and co-workers (3) found the mean total sleep time per 24 hour period to be 4.6 ± 1.6 hours (range 0-7) in 9 post-operative patients. In addition to the reduction in total sleep time, these studies demonstrated altered sleep architecture with a predominance of stage 1 and 2 sleep, decreased or absent stage 3, 4 and REM sleep, shortened REM periods, and sleep fragmentation. Sleep distribution was also abnormal, as up to fifty percent of the total sleep time occurred during the day.

The etiologies of these sleep disturbances in the ICU are presumed to be multifactorial, although little is actually known about the mechanisms responsible for sleep/wake cycle disturbances in the ICU. Environmental stimuli are proposed to be the most disruptive factors to achieving sleep in the ICU (5-11). The environmental stimulus most often cited in the literature to disturb sleep is noise (6,7,12). Several studies have shown that noise levels in the ICU are substantially higher than the Environmental Protection Agency (EPA) recommendations for maximum hospital room noise levels, both at night and during the day (6,7,11-14). Polysomnographic studies evaluating the effect of nocturnal ICU noise on sleep in normal individuals in a sleep laboratory demonstrated decreased total sleep time, total REM time and sleep efficiency, and increased REM latency and arousal index

(number of arousals per hour of sleep) (8,9). However, nocturnal polysomnographic studies of ICU patients have only indirectly linked noise to sleep disruption by attempting to correlate environmental noise levels with arousals from nocturnal sleep (3,5). These studies had small sample sizes and were not designed to determine the specific etiologies of the sleep disruption.

Our previous research has demonstrated that although ICU patients subjectively experienced significantly poorer sleep quality in the ICU than at home, ICU noise was not perceived as the most disruptive environmental stimulus (15). ICU patients perceived frequent interruptions from vital signs and diagnostic testing to be as disruptive to achieving quality sleep as noise, although statistically no single environmental factor was perceived as significantly more disruptive than any other (15). These data led us to hypothesize that other factors besides noise are important in mediating sleep disruption in the ICU.

The main goals of this study were to gain a better understanding of the underlying mechanisms of altered sleep/wake patterns in ICU patients and specifically, to objectively determine the effect of ICU environmental noise on sleep fragmentation. Our study, unlike previous studies, was designed to objectively evaluate the effects of noise on sleep disruption by relaying the output of the noise meter to the polysomnograph so that environmental noise and sleep patterns could be evaluated simultaneously with real time recordings.

Our primary aim was to objectively determine the disruptive nature of environmental noise on sleep in ICU patients. Secondary aims of the study were to: 1) characterize sleep/wake patterns in a group of primarily mechanically ventilated medical ICU patients; and 2) gain insight into the effect of severity of illness on sleep.

METHODS

SITE

This study was performed between March 1997 and February 1999 at the University of Pennsylvania Medical Center and the Presbyterian Medical Center. The study was approved by the Institutional Review Board (IRB) of the University of Pennsylvania.

The medical intensive care unit (MICU) at the University of Pennsylvania Medical Center is a 24 bed ICU with 12 intermediate level of care/step down beds and 12 acute care beds. All of the acute care and step down patient rooms are single patient rooms that are enclosed on 3 sides and can be isolated from the nurses station by a sliding glass door. The ICU at the Presbyterian Medical Center is a 15 bed mixed medical/surgical ICU. All beds are acute care beds. For this study, all of the patient rooms that were utilized were single patients rooms that were enclosed on 3 sides. Seven of these rooms could be totally enclosed by a sliding glass door

while the remaining 4 beds only had a curtain for patient privacy at the entrance to the room.

PATIENTS

All patients were in the ICU for primarily medical problems. Patients were excluded if, prior to the initiation of the study, they were receiving continuous heavy sedation, were stuporous or comatose, and/or had a previous history of dementia. Heavy sedation was defined as the inability to arouse the patient or inability of the patient to follow verbal commands. Heavy sedation was a criterion for exclusion based upon the inability to classify the patients' level of consciousness as sleep versus wakefulness. Patients with a diagnosis of dementia were excluded because of the known abnormal EEG patterns described in demented patients which make it difficult to accurately determine sleep versus wakefulness by EEG criteria even in non-critically ill demented patients (16).

Patients and or their families gave written consent prior to their participation. Patients were volunteers who received no remuneration for their participation.

POLYSOMNOGRAPHY

The gold standard for determining sleep onset and maintenance is polysomnography (17). All subjects were monitored with continuous (24 to 48 hours) of standard polysomnography utilizing a Sandman portable polysomnograph (Nellcor-Puritan Bennet, Canada) or a Biologic portable polysomnograph (Mundelein, IL). Electrode leads were placed on the subject's head in the C3, C4, and 0z positions according to the International 10/20 system of electrode placement. These leads were referenced to two reference electrodes A1 and A2 over the subjects' mastoid regions. Two extraocular (EOG) leads and 2 chin electromyogram (EMG) leads were utilized to assess ocular movements and muscle tone to differentiate REM sleep from NREM sleep and wakefulness. The polysomnograms were scored according to the criteria of Rechtschaffen and Kales (18).

Arousals from sleep were scored according to the American Sleep Disorders Association (ASDA) definition (19). Arousals from sleep specifically due to noise were defined according to the ASDA definition of an arousal and if the arousal occurred during or within 3-seconds after the completion of an environmental noise increase of > 10 dB (A) (see Figure 1).

Figure 1: Polysomnography with 4 channels (C3, C4, O1, O2) of electroencephalography (EEG), right and left electrooculograms (EOG), chin and limb (EMG), EKG and continuous environmental noise recording (mean noise). The EEG represents stage 1 sleep with an arousal caused by a burst of ambient noise measuring 69 (dB)A.

CONTINUOUS ENVIRONMENTAL NOISE RECORDING

Environmental noise was assessed by a Quest 1900 portable integrating/logging sound level meter (Quest Technologies Oconomowoc, WI), which is accurate to within 0.5 decibels (factory manual). A microphone was secured to the head of the bed and positioned so that the microphone was within 3 inches of the patient's head. This technique allowed the microphone to move in harmony with the patient's head in an attempt to measure the noise that the patient was experiencing. Environmental noise was continuously recorded in decibels (dB) on the decibel A (dB{A}) scale. The decibel A scale is a frequency weighting method that simulates the reception characteristics of the human ear (7). The sound meter was calibrated prior to each study with a Quest model QC-20 calibrator at 1000Hz at 94 dB as a reference output. The sound level meter decibel range was set between 40-100 dB (A), based on our preliminary data as well as prior studies

assessing ICU noise levels (5,6,20). The output of the sound meter was simultaneously recorded on the polysomnograph to assess the effect of noise on arousals from sleep (see Figure 1). Noise data for the entire study period was logged and stored at one-minute intervals (the sampling frequency was at 1 second intervals).

ASSESMENT OF SEVERITY OF ILLNESS

Each patient had an Acute Physiology, Age and Chronic Health Evaluation (APACHE) III score calculated for each 24-hour period in an attempt to correlate severity of illness with degree of sleep disruption (21).

STATISTICAL ANALYSIS

Unpaired Student's t-tests were utilized to compare daytime versus nighttime (average, maximum and peak) noise levels, sleep versus wakefulness (average, maximum and peak) noise levels and the non-noise sleep arousal index versus the noise specific arousal index. Unpaired Student's t-tests were also utilized to determine if differences existed between genders and a patient's window status (rooms with versus without windows) with respect to: 1) sleep stages (1, 2, 3/4, and REM); 2) arousal indexes (noise, non-noise and total); 3) daytime sleep (total time and percentage of total sleep time); 4) nighttime sleep (total time and percentage of total sleep time); and 5) total sleep time (TST).

Pearson's correlation analysis and one way analysis of variance were used to determine the relationship of patient age, duration of stay and APACHE III score to the following factors: sleep stages (1, 2, 3/4, and REM), arousal indexes (noise, non-noise and total), daytime sleep (total time and percentage of total sleep time), nighttime sleep (total time and percentage of total sleep time), and total sleep time (TST). Spearman's correlation analysis was used to confirm the Pearson's analysis. Only the Pearson's correlation coefficients were reported if there was an agreement between these latter two analyses.

RESULTS

DEMOGRAPHICS

A total of 24 ICU patients were enrolled between March 1997 and February 1999. Two patients withdrew from the study prior to its initiation at the request from the patients' family members after the initial consent was given. Twenty-two patients completed the study for a total of 30 twenty-four hour periods (8 patients were studied for 48 hours continuously and the remaining 14 patients were studied for 24 hours). The study population was comprised of 12 males and 10 females with a mean age of 61 ± 16 years (range 20 – 83), mean APACHE III score of 57 ± 28 (range 7 - 132) and a mean duration of ICU stay prior to the study of 18 ± 20 days (range 3 – 80). Twenty of the 22 patients were mechanically ventilated at the time of the study, and remained mechanically ventilated for the entire study period.

Primary reasons for mechanical ventilation included: pneumonia (7 patients), sepsis (5 patients), chronic obstructive pulmonary disease (COPD) exacerbation (3 patients), acute respiratory distress syndrome (ARDS) (3 patients) and myasthenia gravis (2 patients). 14 patients received no sedation during the study period. Of the remaining 8 patients, 4 patients received intermittent, as needed, intravenous lorezepam and 4 patients received intermittent, as needed, intravenous doses of fentanyl. No patients were on a combination of benzodiazepines and narcotics during the study period. No patients received tricyclic or other types of anti-depressant medications during the study period. All patients had a Glasgow coma score of 14 or greater upon entrance into the study.

Sleep Architecture and Sleep Distribution

Seventeen (77.3%) of the 22 patients had scorable EEG data according to the criteria of Rechtschaffen and Kales (18). From this group, there were a total of 21 separate 24 hours day/night periods (13 patients with 24 hours of scorable data and 4 patients with 48 hours of scorable data). The other 5 patients (22.7%) demonstrated evidence of septic encephalopathy throughout the majority or all of the study period, and were therefore unable to be scored according to standard criteria of sleep versus wake (see section on sepsis and sleep). Of the 17 ICU patients with scorable sleep/wake polysomnograms, all demonstrated abnormal sleep architecture. Although the mean total sleep time per 24 hour period was within the normal range (8.8 ± 5.0 hrs) (17) there were large individual variations in total sleep time (range 1.7 to 19.4 hrs).

There was a predominance of stage 1 sleep (mean 59 ± 33%) with decreased or absent stages 2 (mean 26 ± 28%), 3/4 (mean 9 ± 18%) and REM sleep (mean 6 ± 9%). Twelve of these 17 patients demonstrated no REM sleep. Of the 8 patients who were studied continuously for 48 hours, 5 had scorable EEG data. There were no significant differences between study day 1 and 2 with respect to mean total time spent in sleep stages 1, 3/4, and REM, day vs. night total sleep times or the overall arousal index. There were no significant differences ($p > 0.05$) between genders or window status with respect to TST/24 hour period in time in any sleep stage. There were no significant correlations ($p > 0.05$) between TST/24 hour period or time in any sleep stage with age, duration of ICU stay, or APACHE III score.

Sleep Disruption and Arousal Index

All 17 patients with scorable sleep/wake stages demonstrated nonconsolidated sleep that was distributed throughout the 24 hour day-night study period (see Figure 2). Fifty-seven percent ± 18% of the total sleep time occurred during the daytime (6AM – 10 PM) and 43% ± 18% of the TST occurred during the nighttime hours (10PM – 6AM). The mean number of sleep periods per 24 hour study period was 41 ± 28 (range 5 - 100). The mean length of each sleep bout was 15 ± 9 minutes (range 5.5 - 40 minutes). REM sleep, when it occurred, was equally

distributed between day (50% ± 5%) and night (50% ± 5%). The overall arousal index (number of arousals per hour of sleep) was normal (mean 11.6 ± 5.0; range of 4.6-21.2) (22). There were no significant differences ($p > 0.05$) between genders or window status with respect to daytime vs. nighttime sleep or the overall arousal index. Age, duration of ICU stay, and APACHE III score were not significantly correlated ($p > 0.05$) with daytime vs. nighttime sleep or the overall arousal index.

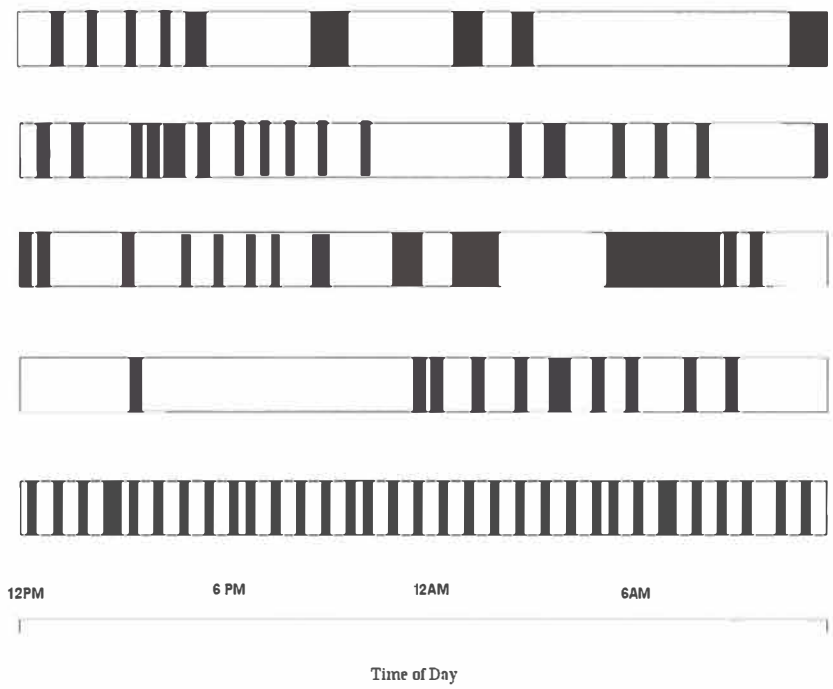

Figure 2: Schematic representation of the redistribution of sleep and wake in 5 subjects over the 24 hour period. Black areas represent episodes of sleep and white areas represent wakefulness.

The Effect of Environmental Noise on Sleep Disruption

The mean, mean maximum and mean peak ICU environmental noise levels exceeded EPA recommendation during both the daytime and nighttime hours. There were no statistically significant differences ($p > 0.05$) in mean (59.1 ± 6.1 dB[A] vs. 56.8 ± 4.9 dB[A]), mean maximum (68.5 ± 7.7 dB vs. 64.6 ± 7.5 dB) or mean peak (85.9 ± 5.1 dB vs. 82.8 ± 5.3 dB) noise levels between the day and night, respectively. There were no statistically significant differences ($p > .05$)

between mean (58.9 ± 6.0 dB vs. 57.1 ± 5.2 dB), mean maximum (68.3 ± 7.5 dB vs. 64.9 ± 7.6 dB) and mean peak (85.6 ± 5.0 dB vs. 84.9 ± 4.8 dB) noise levels during periods of sleep and wakefulness.

Overall, 11.5% of the arousals from sleep for the entire population studied were secondary to environmental noise. Arousals related to environmental noise comprised an average of 11.5 ± 11.8 % of the total arousals from sleep per subject. The mean arousal index specifically related to environmental noise was 1.9 ± 2.1. This was significantly less ($p<0.0001$) than the mean spontaneous (non-noise) arousal index of 9.6 ± 4.9. Overall, environmental noise was responsible for 17% of the awakenings from sleep. Awakenings related to environmental noise comprised an average of 26.2% ± 24.8% (range 0% - 75%) of the total awakenings from sleep per subject. There were no significant differences ($p > 0.05$) between genders or window status with respect to the noise specific arousal index or awakenings secondary to noise. Age, duration of ICU stay, and APACHE III score were not significantly correlated ($p > 0.05$) with the noise specific arousal index or awakenings secondary to noise.

The Effect of Sepsis on Sleep and Wake States

As stated earlier, 5 patients either developed sepsis and/or positive blood cultures during the study period (4 of 5) or were recovering from sepsis (1 of 5) during the study period. None of the patients were receiving continuous sedative medications immediately before (previous 24 hours) or during the study period. All 5 patients demonstrated similar EEG patterns of a baseline of low voltage mixed frequency waves with intermittent and variable amounts of theta and delta waveform activity (See Figure 3). In the 4 patients without known sepsis prior to the study period, this EEG pattern appeared up to 8 hours prior to these patients demonstrating clinical signs of sepsis (fever, hypotension). This EEG pattern was present both when the patients' eyes were open as well as when they were closed. For this reason, we were unable to define the patients' state of consciousness into definitive sleep or wake states, by current EEG criteria. These 5 patients did not demonstrate any evidence of clearly definable sleep throughout the study period. There was no evidence of spindles, K-complexes or REM activity, all hallmarks or normal sleep.

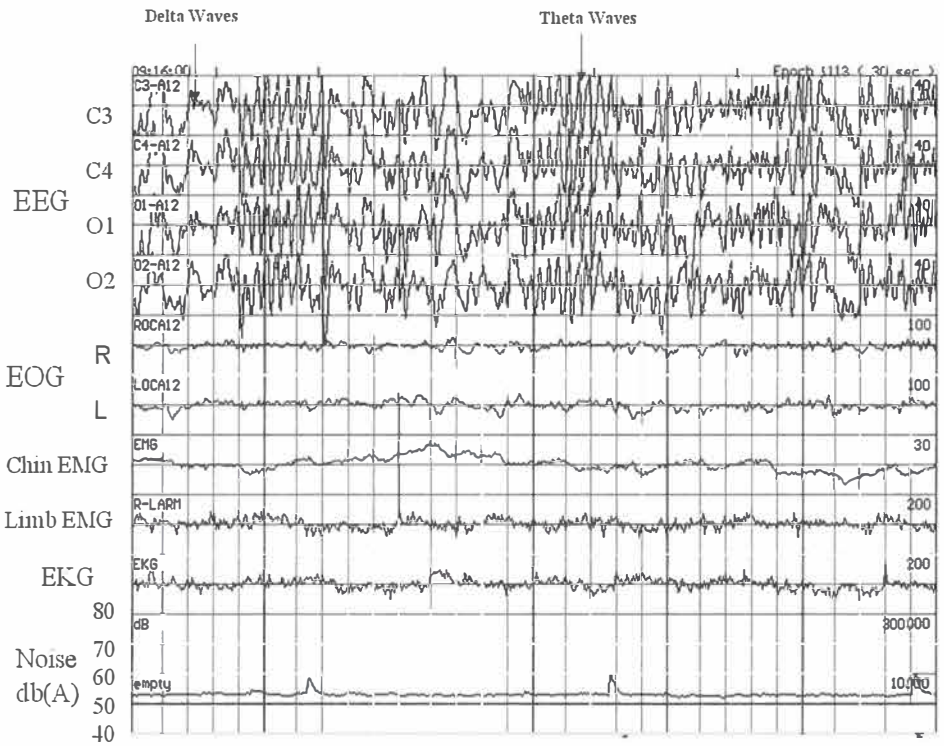

Figure 3: Polysomnographic representation of septic encephalopathy. This EEG pattern demonstrates of a baseline of low voltage mixed frequency waves with intermittent theta and delta waveform activity

DISCUSSION

All medical ICU patients studied demonstrated sleep/wake cycle abnormalities. Non-septic ICU patients demonstrated abnormal sleep architecture with a predominance of stage 1 sleep and decreased or absent stages 2, 3, 4 and REM sleep. These patients tended to sleep for frequent, short periods that were non-consolidated and abnormally distributed over the 24-hour day. ICU patients with sepsis demonstrated varying degrees of encephalopathy, with no definable sleep or wake periods. Although environmental noise was in part responsible for sleep/wake abnormalities, our data suggested that other factors must be responsible for sleep disruption in this patient population. Finally, although further research needs to be performed, we have observed that continuous EEG monitoring may be useful as an early marker of the onset of sepsis.

LIMITATIONS

Our study design had several limitations, which should be reviewed. Our results are not generalizable to all ICU patient populations as the majority of the patients that we evaluated were non-sedated mechanically ventilated medical ICU patients. However, this is a very important patient population to study since many ICU patients are mechanically ventilated. There may also have been a selection bias as the patients were selected to participate based on their likelihood of remaining in the ICU for a continuous 48 hour period and were therefore not randomly selected. We did not control for underlying disease state as we were interested in evaluating disorders of sleep and wake in a heterogeneous population of ICU patients. We excluded patients under heavy sedation in this initial study because we thought it would be difficult to classify a given patient's level of consciousness as wakefulness vs. sleep. Also, sedatives themselves can affect sleep and/or the EEG potentially confounding our results (23). However, the majority of our patients were not treated with sedatives. We were unable to determine if all of the patients' sleep/wake cycles changed on a day-to-day basis or improved over time as we evaluated each patient only for 24-48 hours and did not control for length of stay in the ICU. However, the abnormalities in sleep architecture were evident regardless of length of stay, suggesting that length of stay may not be an important contributor to sleep alterations in the ICU. Also, there were no significant differences in the total sleep time, time in the various sleep stages, or day vs. night total sleep times between study day 1 and 2 in the 5 patients with scorable EEG data who were studied for 48 continuous hours. This suggests that there is little day-to-day variation in sleep architecture.

ETIOLOGIES OF SLEEP DISRUPTION

Environmental noise clearly plays a role in disrupting sleep in medical ICU patients. The finding that environmental noise was not responsible for the majority of arousals and awakenings from sleep is contrary to the current literature which considers noise to be the major etiologic factor responsible for sleep disruption in the ICU (5-11). We have objectively demonstrated that environmental noise was responsible for 11.5 % and 17% of the arousals and awakenings from sleep, respectively. These findings confirm our previous research that demonstrated that although ICU patients subjectively experienced significantly poorer sleep quality in the ICU than at home, ICU noise was not perceived as the most disruptive environmental stimulus (15).

We believe our results are valid for several reasons. First, our technique of simultaneously monitoring environmental noise and polysomnography allowed for the objective measurement of effects of noise on sleep. Second, there were no significant differences in mean, maximum or peak noise levels during periods of wake and sleep, so our results can not be explained by differences in noise levels during sleep versus wake periods. Finally, it can not be argued that our ICUs were quieter than other ICUs as the noise levels recorded in our ICUs appear to be comparable to those in other publications (7,24).

The finding that environmental noise was not as disruptive to ICU patient sleep as previously described in the literature was not completely surprising. Previous studies show that there are wide variations in individual sensitivity to sounds during sleep and that the meaning of the sound is also critical (25,26). Although studies on the acute affect of noise on sleep have consistently demonstrated a sleep disrupting effect, normal individuals rapidly adapt to the disruptive effects of environmental noise on sleep (27). Studies in normals have demonstrated that individuals habituate to sound by increasing their arousal threshold for noise over time, with some individuals being able to increase their arousal threshold for noise to more than 80 dB(A) (28-30). This finding is also consistent with the results of Aurell et al. (3) who demonstrated that sleep architecture and distribution were significantly altered in 9 post-surgical ICU patients, despite a concerted effort by the staff to keep environmental disturbances (noise, interruption and light) to a minimum.

From the standpoint of the ICU environment, we previously described that ICU patients subjectively perceived human interventions and diagnostic testing to be as disruptive to sleep as noise (15). In this predominantly mechanically ventilated group of patients, it is possible that sleep was disrupted by patient/ventilator dyssynchrony as well as from human interventions such as suctioning and the administration of respiratory treatments. This study was not designed to evaluate the effects of human interventions or other factors (light, noxious odors, etc.) on sleep/wake disturbances. Future research should focus on objectively determining the effects of these factors on sleep disturbances in the ICU population.

It was remarkable that the abnormal sleep/wake patterns and sleep disruptions attributable to noise demonstrated by this group of patients was not affected by patient age, gender, duration of ICU stay or severity of illness. These findings confirm our previous research (15), which demonstrated that the patient characteristics of age, gender and duration of stay were not associated with an ICU patient's poor subjective sleep quality. This indicates that all mechanically ventilated medical ICU patients are at risk for sleep disturbances. This also indicates that other factors, environmental (human interventions and light) and/or patient specific (medications, pain/anxiety, underlying disease, inflammatory mediators, and/or circadian rhythm disturbances) must be responsible for sleep/wake disturbances in the ICU.

Abnormalities of Sleep Architecture

Although the majority of the critical care literature (1-4) has suggested that ICU patients are sleep deprived, we have demonstrated that mechanically ventilated medical ICU patients are not necessarily quantitatively sleep deprived. Our patients demonstrated large variations in total sleep time per 24 hour period, with a mean total sleep time per 24 hour period of 8.8 ± 5.0 hours. Many patients are selectively deprived of certain stages of sleep, but our patients were not totally sleep deprived for any given 24-hour period.

Although ICU patients may not be quantitatively sleep deprived, they all demonstrated fragmentation and non-consolidation of their sleep/wake cycles as well as a predominance of stage 1 sleep. Thus, they may be functionally sleep deprived. The sleep continuity theory demonstrates that consolidation of sleep is as important as total sleep time, as decrements in daytime function increase as the length of periods of consolidated sleep decrease (28-30). It is likely that many of these patients suffer from chronic daytime and/or nighttime sleepiness as well as neurocognitive performance deficits that are common in individuals experiencing sleep fragmentation (28-30).

ICU patients appear to lose the ability to maintain the normal circadian night/day distribution of sleep and wake. Our data indicate that total sleep time is redistributed over a 24 hour period with large individual variations in total sleep time. These data are in agreement with other studies evaluating sleep in the ICU with continuous polysomnography (7,31). Our results reinforce the importance of performing sleep studies over a 24 hour period to adequately characterize sleep/wake patterns in this patient population as it is evident that studying nocturnal sleep alone is insufficient.

Decreased or absent REM sleep as well as its equal distribution across the day and night is abnormal. REM sleep typically occupies 20 – 25% of nocturnal sleep time in normal individuals and unlike delta sleep, REM distribution remains relatively stable throughout the life-span (17). The mechanisms responsible for the absence or abnormal distribution of REM sleep in critically ill patients is unknown, but may be explained by: 1) inadequate time during short bouts of sleep to cycle into REM sleep (17); 2) disturbances in the circadian system which normally controls the timing of REM sleep in normal individuals (32, 33); and 3) underlying disease and specifically mediators (endotoxin) that may be released with inflammatory states/sepsis which may decrease or inhibit REM sleep (34,35). This may help to explanation why our septic subjects did not demonstrate any REM activity. We do not believe that medications were responsible for the REM suppression demonstrated by this group of patients as the majority (84%) of the patients studied were not on REM suppressing medications.

Sepsis and Sleep

This study also provides insight into the effects of sepsis on sleep and wake states. The finding of EEG slowing with sepsis states is most consistent with septic encephalopathy (35). Interestingly, our patients with sepsis demonstrated no evidence of clearly definable sleep or wake by standard monitoring criteria over the 24-48 hour monitoring period. Patients with underlying sepsis appear to be in a dissociated state of consciousness, deprived of both normal sleep and wake states. Although not previously described in older studies evaluating sleep in ICU patients (2-4), Cooper et al. (31), recently described similar findings in a group of mechanically ventilated patients with acute lung injury. It is likely that many ICU patients may demonstrate a similar state of dissociated consciousness.

Although EEG changes with previously diagnosed sepsis have been described in the literature (36-38), the observation that these EEG changes may precede other clinical features of sepsis (fever, tachycardia, hypotension) is a novel finding. Five of the 22 patients demonstrated EEG findings that were consistent with mild to moderate encephalopathy, before other signs of sepsis were present. None of the non-septic patients demonstrated this EEG pattern. Futures studies will need to be prospectively performed to determine if continuous EEG will be a valid, non-invasive marker of early sepsis.

CONCLUSIONS

Our data indicates that mechanically ventilated medical ICU patients manifest sleep/wake pattern abnormalities. ICU patients demonstrate large individual variations in total sleep time and, in general, are not quantitatively sleep deprived. Sleep architecture and distribution are severely altered as illustrated by excessive sleep fragmentation, selective sleep stage deprivation and loss of the normal circadian night-day, sleep-wake cycle distribution. Although all of the mechanisms responsible for these sleep/wake abnormalities are not yet elucidated, it appears that the impact of environmental noise on sleep disruption is much less important than previously described. Our data also indicate that all patients are at risk for sleep/wake disturbances as age, gender, severity of illness and duration of stay were not associated with sleep/wake abnormalities. Further research is needed to better define the mechanisms responsible for sleep abnormalities in patients who are critically ill.

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Chapter 3

Circadian Rhythmicity in Intensive Care Unit Patients

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American Thoracic Society International Conference San Diego, California, U.S.A. (2004)

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Intensive Care Unit (ICU) patients are thought to have abnormal circadian rhythms. To investigate circadian rhythms in the ICU, we studied core body temperature over a 48-hour period in 21 patients (59±11 years; 8 males vs. 13 females). The circadian phase position for 17 of the 21 patients fell outside the normative range for variability among healthy normals. In 10 patients, the circadian phase position fell earlier than the normal range; in 7 patients, the circadian phase position fell later than the normal range. The mean ± SD of circadian displacement in either direction (advance or delay) was found to be 4.44 ± 3.54 hours. There was no evidence for significant day-to-day variation of the 24-hour temperature profile within each patient. Stepwise linear regression was performed to determine if age, gender, APACHE III score, or day in the ICU could predict the patient-specific magnitude of circadian displacement. APACHE III score was the only variable found to be significantly predictive of circadian displacement. The findings indicate that circadian rhythms are present but altered in ICU patients.

Almost all human physiologic processes exhibit circadian (i.e., near-24-hour) rhythms reflecting the synchronization of the body's functions with each other and with the external environment. The suprachiasmatic nuclei (SCN) in the hypothalamus contain the biological clock that drives the body's circadian rhythms [1;5;6]. In normal subjects, environmental time cues such as the light-dark cycle entrain (i.e., synchronize) circadian rhythms, keeping them at a relatively constant 24-hour period with a fixed temporal relationship to the environment. When left unsynchronized, the circadian pacemaker tends to drift, having an intrinsic period of about 24.2 hours on average in human beings [7].

The circadian clock cannot be measured directly in humans, so surrogate markers have been used to measure its output. Under controlled circumstances, core body temperature (CBT), which is higher during the day than during the night; and plasma melatonin, which displays a pattern opposite to that of CBT, are considered the most reliable physiologic markers of circadian rhythmicity [1;2;4;10;24;32]. Plasma cortisol has also been used as a circadian indicator, but recent studies have cast doubt on the robustness of cortisol as a marker of circadian rhythmicity in humans [49-52].

Limited data evaluating circadian rhythms in the ICU have suggested that these rhythms are considerably aberrant in patients [2-4;8-10]. Two retrospective studies [2;4], evaluating circadian rhythms in ICU patients using CBT recordings, showed an absence of circadian rhythmicity in 20% and 80% of ICU patients, respectively. The remaining patients showed large within-subject variability not normally observed in healthy individuals [11]. Such altered circadian rhythms may have important physiologic ramifications. For example, circadian rhythm changes have been shown to adversely affect respiratory muscle performance [12-15]. Furthermore, the efficacy, half-life and toxicity of medications are influenced by circadian rhythms [16-19]. Normal circadian rhythmicity is thought to be beneficial for recuperation from medical conditions [17;18]—understanding circadian rhythms

and their possible alterations in patients may therefore be important for health care in the ICU [8;9;20].

The primary goals of the present study were to identify any abnormalities in the timing of the circadian rhythm as measured by CBT, while taking into account masking factors potentially affecting CBT; and to find medical and/or demographic correlates of such abnormalities. We hypothesized that circadian rhythms in ICU patients would be significantly different than normal controls.

METHODS

Subjects

Core body temperature (CBT) was measured in 28 patients in the ICU at the University of Pennsylvania Medical Center (UPMC) in Philadelphia, Pennsylvania; in the ICU at Presbyterian Medical Center (PMC) in Philadelphia, Pennsylvania; and in the ICU at the University Medical Center Groningen (UMCG) in Groningen, The Netherlands. The facility at UPMC is a medical ICU with 12 acute care beds and 12 "intermediate level care" or step down beds; the facility at PMC is a mixed medical and surgical ICU with 15 acute care beds; and the facility at HUG is a mixed medical and surgical ICU with 12 acute care beds. This study was approved by the Institutional Review Board of the University of Pennsylvania as well as the Medical Ethical Committee of the UMCG. Patients or their legally authorized representatives gave written consent prior to participation.

Recordings

CBT recordings were made for 48 hours at a rate of one sample every 5 minutes. CBT was measured with a temperature-sensing Foley urinary catheter (C.R. Bard, Inc., Covington, GA) in 11 patients and with a Mallinckrodt 12 French temperature-sensing rectal probe (Mallinckrodt, Inc., St. Louis, MO) in 10 patients. Urinary bladder temperature monitoring is a well-investigated and validated method to determine CBT, with low likelihood of being accidentally extruded and a high degree of accuracy [21-24]. Rectal temperature probes have also been successfully utilized and validated in numerous investigations of CBT [25;26]. During the 48-hour study period, patients were monitored not to be hypothermic or febrile, and they did not receive any antibiotics, non-steroid anti-inflammatory drugs (NSAIDs), aspirin, corticosteroids or any other medications that would have suppressed a potential fever. For all ICU patients, Acute Physiology And Chronic Health Evaluation III (APACHE III) [27] scores were assessed on the first day of CBT registration.

Analyses

First, hourly averages of CBT were computed for each subject. The first 24 hours were labeled "day 1" and the second 24 hours were labeled "day 2." Subsequently, the data were analyzed with repeated-measures analysis of variance (ANOVA) in a

time (24 levels) × day (2 levels) design, in order to evaluate the day-to-day variation of the 24-hour CBT profile.

Contingent upon the absence of significant day-to-day variation, a harmonic regression model of two sinusoids—with a fundamental period of 24 hours and a harmonic period of 12 hours, respectively—was fitted to the individual patients' original 48-hour time series (i.e., the 5-minute samples, not the hourly averages. As a marker of the circadian phase position of the rhythm in CBT, the clock time of the CBT minimum in the regression model was assessed. In addition, the CBT range was determined as the difference between the minimum and the maximum in the regression model.

For each patient, circadian phase position values were compared to a database of healthy, extreme morning- and evening-type individuals studied under constant-routine conditions [26]. This database was previously established to expose the boundaries of inter-individual variability in circadian phase among healthy individuals [26], and may therefore serve as a reference for circadian abnormalities. For patients in the present study who had a circadian phase position of the CBT minimum that was outside the reference interval, which ranged from 04:38 to 06:45, the absolute time difference between the observed circadian phase position and the nearest boundary of the reference interval was computed as a measure of the magnitude of circadian displacement. This circadian displacement was a primary outcome measure of the study.

To assess associations of demographic and medical variables with the degree of circadian displacement, correlation analysis (Pearson's r) and stepwise linear regression were performed. Finally, one-way ANOVA was employed to detect differences in circadian displacement among disease categories (renal insufficiency, myastenia gravis, COPD exacerbation, or ARDS), and between mechanically ventilated versus non-ventilated patients.

RESULTS

Seven of the 28 patients where excluded from the analyses because a fever (CBT > 38 °C) developed in the 5 days before or during the study period, leaving a group of n=21 ICU patients. Of these 21 patients, 9 were hospitalized in the ICU at the UPMC in Philadelphia, Pennsylvania; 6 were hospitalized in the ICU at PMC in Philadelphia, Pennsylvania; and 6 were hospitalized in the ICU at the UMCG in Groningen, The Netherlands. Seventeen out of the 21 patients were on mechanical ventilation; all were tube fed. Table 1 summarizes the demographic and medical information of the study population.

Number of subjects (n)	21
Age (mean ± SD), (range {min. - max.})	59 ± 11, (33-75)
Male vs. female	8 vs. 13
APACHE III (mean ± SD), (range {min. - max.})	49 ± 22, (29-95)
Mechanically ventilated	17
Renal insufficiency	10
Myastenia gravis	3
COPD exacerbation	6
ARDS	2
First day of CBT recording relative to day of ICU admission (mean ± SD), (range {min. - max.})	19.9 ± 18.9, (2-45)

Table 1 summarizes the demographic and medical information of the study population.

Repeated-measures ANOVA of the hourly averages across the 48 hours of CBT recording in all 21 patients showed no significant effects for day ($F[1,20]=0.045$, $P=0.84$) and for time by day interaction ($F[23,460]=0.809$, $P=0.54$). Thus, there appeared to be little day-to-day variation of the 24-hour CBT profile within each patient. Analyses were therefore continued by fitting a harmonic regression model to each patient's CBT time series. The 24-hour rhythm component of CBT was statistically significant in each subject ($P<0.001$; see ref. [28]). The range between the minimum and maximum of CBT was found to be 0.82 ± 0.60 ºC. The mean ± standard deviation (SD) for the circadian phase position, as estimated by the timing of the CBT minimum in the regression model, was 10:07 (HH:MM) ± 417 min.

The individual subjects' circadian phase positions are shown in Figure 1. Substantial inter-individual variability in the timing of the CBT rhythm was observed—circadian phase position values spanned almost the entire 24 hours of the day. A Kolmogorov-Smirnov test confirmed that the distribution of circadian phase positions of the CBT rhythm was not significantly different from a uniform distribution across the 24 hours of the day ($Z=1.12$, $P=0.16$). This indicates that the minimum of CBT was not consistently anchored in the early morning hours, as is typical for healthy normal individuals, but could be positioned at any hour of the day. This finding demonstrated that the timing of circadian rhythms was abnormal in the ICU patients.

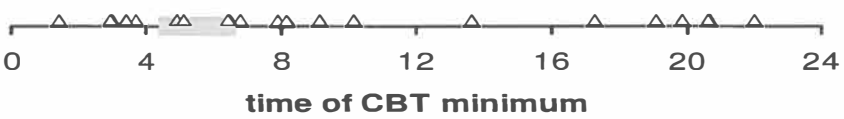

Figure 1. Individual patients' circadian phase positions (triangles) as determined by the estimated minimum of core body temperature (CBT), and reference interval for healthy normals (gray bar), plotted against clock time (in hours). Data from all 21 ICU patients included in the study are shown; some individuals' circadian phase positions overlapped. The boundaries of the reference interval (04:38 to 06:45) were taken from a database of healthy extreme morning- and evening-type individuals studied under constant-routine conditions similar to the ICU [26]. The vast majority of healthy normals would be expected to have circadian phase positions inside this relatively narrow reference interval. In contrast, the ICU patients' circadian phase positions were distributed over the entire 24 hours of the day.

For 17 of the n=21 patients, the circadian phase position fell outside the reference interval for healthy normals (gray bar in Figure 1) between 04:38 and 06:45 [26]. The mean ± SD of circadian displacement, defined as the absolute deviation from the nearest boundary of the reference interval, was 4.44 ± 3.54 hours for these 17 patients. For 10 of them, the circadian phase position was closest to the early boundary of the reference interval (i.e., 04:38), suggesting that the circadian rhythm in these patients was relatively advanced. For the remaining 7 patients, the circadian phase position was closest to the late boundary of the reference interval (i.e., 06:45), which suggested that the circadian rhythm in these patients was relatively delayed.

Stepwise linear regression yielded APACHE III score as the only variable to be significantly predictive of circadian displacement ($F[1,19]=24.4$, $P<0.001$). Higher APACHE III scores were associated with larger circadian displacements, as shown in Figure 2. One-way ANOVA revealed a trend for an effect of mechanical ventilation ($F[1,19]=3.81$, $P=0.066$): the mean ± standard error of circadian displacement was 0.61 ± 0.35 hours for the 4 non-ventilated subjects, and 4.30 ± 0.90 hours for the 17 mechanically ventilated subjects. No statistically significant differences in circadian displacement were found among the different disease categories ($F[3,17]=0.325$, $P=0.81$)

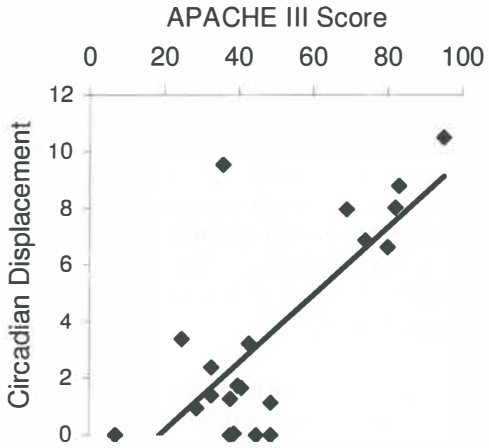

Figure 2. Scatter plot of APACHE III score versus circadian displacement (in hours) in all 21 subjects, with trend line. Higher APACHE III scores were associated with greater circadian displacement.

DISCUSSION

The main finding of this study was that, while circadian rhythms were detectable in the CBT recordings of every ICU patient, they showed abnormal circadian phase positions, with circadian displacement being greatest in patients with the highest APACHE III scores. Out of the 21 patients, only four had a circadian phase position of the CBT minimum that fell inside the reference interval for healthy normals as anchored by extreme morning- and evening-type individuals. No significant relationship was observed between circadian phase position and length of time in the ICU.

The result of altered circadian phase positions in ICU patients confirms the findings of two earlier studies in the ICU [2;4]. Tweedie et al. [4] showed that the timing of the peak of the circadian rhythm in CBT varied substantially between patients and within patients, with changes of several hours from day to day, in a group of 15 patients who spent at least 8 days in the ICU. Dauch and Bauer [2] recorded the CBT profiles of 31 patients suffering from severe cerebral damage, showing only 20% to have a sinusoidal shape in their CBT profile. This latter result is questionable, however, as it was based on "empirical measures" [2] rather than proper statistical evaluation of the data. Our results differed from these studies in that we observed only small day-to-day differences in the timing of peak CBT within patients. This may be a consequence of the various steps we took (e.g., exclusion of febrile patients as well as those with fever-reducing medications) to limit masking effects on CBT recordings (as discussed earlier).

Etiologies of Abnormal Circadian Rhythms in the ICU

Our finding that the circadian phase position of the CBT rhythm was more aberrant with greater APACHE III scores suggests that severity of illness may directly or indirectly contribute to changes in circadian rhythms in ICU patients. Altered circadian phase positions in ICU patients may also result from abnormal temporal cues (zeitgebers) in the ICU environment, which can cause desynchronization of the circadian pacemaker. Indeed, studies have suggested that zeitgebers are abnormal in the ICU [8;9;20]. Light patterns in particular appear to be different for ICU patients compared to normal controls [9]. Properly timed environmental light is a potent zeitgeber in human beings—but if ICU patients receive insufficient and/or improperly timed light, changes in the circadian rhythmicity may result like those observed in the present study.

In the context of circadian abnormalities, it is noteworthy that patients in the ICU also have abnormal sleep-wake patterns [8;41-46]. ICU patients tend to sleep in short bouts approximately evenly dispersed over day and night. Whether or not the sleep-wake pattern influences circadian rhythmicity directly is not clear [33], but sleep is also associated with shielding from light exposure due to eye lid closure. Thus, even if light levels on the ICU are not disruptive for circadian rhythms per se, diurnal sleep bouts may still result in abnormal light exposure and consequently disrupt circadian rhythmicity.

Effects of Abnormal Circadian Rhythms

Altered circadian rhythmicity may play a role in the pathogenesis of abnormal sleep-wake patterns. Noise can be disruptive to sleep in the ICU, but it was found not to be the only sleep disturbing factor [8]. In view of the normal regulatory relationship between circadian rhythmicity and sleep propensity, our finding of significantly altered CBT rhythms in ICU patients could help explain why sleep is abnormal in the ICU. If sleep is beneficial for clinical recovery, as is widely believed, then it may be worthwhile to investigate means to normalize circadian rhythms in the ICU, as this may lead to reduced sleep disruption.

Knowledge of the circadian phase position in critically ill patients may have direct physiologic and therapeutic implications beyond the regulation of sleep. For instance, peripheral and pulmonary muscle strength vary across the circadian cycle [12;34-37]. Peak pulmonary function occurs in the late afternoon, and pulmonary function is most reduced at approximately 04:00 at night [38]. Chronic obstructive pulmonary disease (COPD) patients show circadian fluctuations in pulmonary function as well, with circadian differences between peak and trough values of FEV1 (forced expiratory volume in 1 second) and peak expiratory flow rates as large as 25–50% [16;19;38;39]. It may thus be useful to wean mechanically ventilated patients, especially those with COPD, when respiratory muscle strength is at its circadian peak. This time may be predictable based on the temporal relationship between the pulmonary function rhythm and the CBT rhythm. Patients

at risk for respiratory failure with little physiological reserve may benefit from circadian rhythm-tailored weaning strategies.

Studies have also shown that drug efficacy and half-life are dependent on circadian timing [16;17;47]. The use of chronotherapy (the administration of drugs at specific circadian times) in the ICU may benefit patients by potentially enhancing drug efficacy and/or decreasing toxicity [16-19;47;48]. Since CBT rhythms appeared to be relatively stable across days in our 48-hour study period, and are comparatively easy and inexpensive to measure, CBT recordings could be useful as a circadian marker in future research to evaluate the efficacy of circadian-based drug delivery strategies. Appropriately timed patient care and/or circadian realignment strategies may positively influence patient outcomes in the ICU.

Limitations

We had several limitations in this study that need to be discussed. We had a relatively small number of subjects that were studied. Nonetheless we were still about to demonstrate significant differences in ICU patients' circadian rhythms compared to controls so we do not believe the sample size should be an issue. Our control group was normal subjects and they were not residing in the ICU. Future studies should examine the circadian rhythm of normal subjects undergoing ICU protocols. We required patients to be on stable ventilatory setting, afebrile, and off any fever-reducing medications prior to enrollment in the investigation—so as to minimize masking effects on CBT measurements. Therefore, most patients were studied several weeks into their hospital stay (20 days on average) and were potentially in the recovery period of their illness. This limited overall severity of illness as measured by APACHE III scores (which were calculated at the start of CBT recording), and the present results may not generalize to more severely ill patients. Even so, despite the relatively moderate severity of illness in the study sample, we observed substantial circadian displacement in our patients.

We only used one circadian phase marker in this study. We selected CBT rather than plasma melatonin as a marker because melatonin secretion is suppressed by light exposure. Previous research has shown that light patterns in the ICU are abnormal and elevated at night [9], and sleep (and therefore eye closure) is fragmented and distributed across the entire day [8]. As a consequence, there is considerable potential for confounding effects ("masking") on plasma melatonin profiles due to light exposure in the ICU. Furthermore, the effects on melatonin levels of medications typically used to treat patients have not been comprehensively studied, and melatonin has not yet been established as a reliable circadian marker in the ICU by other investigators.

There are several factors that result in masking effects on CBT profiles. Changes in ambient temperature affect CBT profiles [4, 24], but ambient temperature in the ICU varies little due to active climate control. Physical activity and postural changes also influence CBT [30], but ICU patients are not physically active, and typically undergo postural changes by standardized protocols (head of bed is elevated 30

degrees) and our patients were not upright. The onset of sleep is associated with a gradual drop in CBT [31], and the occurrence of wakefulness gradually reverses this effect; however, the sleep-related effect can only fully develop if sleep is consolidated. In ICU patients, sleep and wakefulness are very fragmented and almost evenly distributed over the 24 hours of the day [8], so that masking from sleep is unlikely to occur systematically. Food intake has been found to affect CBT as well 29], but when ICU patients are tube fed this effect should be eliminated. Each of our patients were tube fed according to the same algorithms. Finally, hypothermia and fever (or fever-reducing medications) may mask circadian rhythmicity in CBT, but these effects were avoided since we selected patients who are neither hypothermic nor febrile. Our patients did not develop fever during the 48 hours they were studied, Light levels, which can affect circadian rhythms, were not controlled in this investigation, However, the goal of this study was not to examine the effect of light on circadian rhythms and the light levels were the same for each patient in each hospital.

Conclusions

In conclusion, we demonstrated that the circadian rhythm of CBT in critically ill ICU patients tends to be considerably shifted relative to normal controls. Patients with higher APACHE III scores showed greater circadian phase displacement. However, circadian rhythmicity was relatively stable within patients over 48 hours of recording. Increased knowledge and consideration of patients' circadian rhythmicity could have a positive impact on therapeutic interventions (e.g., drug administration, weaning) and the quality of sleep in the ICU. Although the causes of circadian abnormalities were not elucidated by the present study, and further research is necessary, the finding of abnormal circadian rhythms in the ICU strongly suggests that treatment strategies aiming to realign circadian rhythms may be beneficial for clinical recovery in critically ill patients.

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Chapter 4

Light–Dark Patterns in the Intensive Care Unit

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The intensive care (ICU) environment is often regarded as one of near-constant lighting, although there is little objective data on light levels in the ICU. The issue is important, as light is a synchronizer of the suprachiasmatic nuclei in the hypothalamus (the circadian pacemaker), where the body's circadian rhythms are orchestrated. ICU patients have been documented to have abnormal circadian rhythms. To investigate if ICU light patterns could underlie these circadian rhythm disturbances, we studied patients' light exposure over a 48-hour period in two different hospitals (n=36) and in healthy non-hospitalized controls (n=12). We found that ICU light–dark patterns were generally not comparable to those of the control subjects. In comparison to controls, ICU patients were exposed to lower light levels during the day and higher light levels during the night. Although significant day–night variations in ICU light levels were present, and relatively stable across the two days of the study period, the amplitude of the day–night differences in light exposure was smaller in ICU patients than in the non-hospitalized controls. Further research should determine whether such abnormal light exposure is the actual cause of circadian rhythm disturbances in ICU patients, and if managing light exposure can help overcome these disturbances.

Human physiologic processes exhibit near-24-hour rhythms reflecting the synchronization of the body's functions with each other and with the external environment. Examples of these circadian rhythms are the variation of core body temperature (CBT) over the day, the nocturnal secretion of melatonin, and the daily alternation of sleep and wakefulness (1-3). Measurements of these variables have revealed significant circadian abnormalities in intensive care unit (ICU) patients (4-11). To date, there is no evidence-based explanation for these abnormalities. In this paper, we investigate whether light exposure could be a factor underlying circadian disruption in the ICU.

It has been hypothesized that normal circadian rhythmicity would be beneficial for recuperation from medical conditions (12,13). Conversely, altered circadian rhythms may have clinically relevant physiologic ramifications. From research on shift workers, for instance, it is well known that alterations in circadian rhythmicity causes sleep problems (14). Likewise, circadian abnormalities may be the cause of scattered sleep–wake patterns observed in the ICU (7). In turn, such sleep disturbances may adversely affect respiratory muscle performance (15-18). It is also noteworthy that the efficacy, half-life and toxicity of medications vary over the day (12,13,19-21). For all these reasons, understanding circadian rhythms and identifying cause(s) of circadian rhythm disturbances may be critically important for clinical outcomes in ICU patients.

Although little is known about the mechanisms responsible for circadian abnormalities in the ICU, environmental stimuli are thought to be involved (22-25). Light exposure plays a dominant role in synchronizing (entraining) endogenous circadian rhythmicity to the 24-hour day (26,27). Even dim indoor light has been shown to affect the circadian pacemaker (28-30). Previous studies have not determined definitively if light patterns in the ICU are normal, and whether or not

they effectively entrain patients' circadian rhythms. The only previous study systematically evaluating environmental light conditions in the ICU (31) concluded that light exposure reflected a normal photoperiod. However, this study measured light levels between patients' bed and room window and not at eye level.

The present study was designed to investigate more accurately whether light levels in the ICU as experienced by the patients differ significantly from the light–dark cycles to which normal controls are exposed. In addition, differences in environmental light patterns between ICU rooms with windows and ICU rooms without windows were examined, so as to gain insight into the influence of natural versus artificial light in the ICU.

METHODS

Light exposure was measured in the ICU at the Hospital of the University of Pennsylvania (HUP) and in the ICU at Presbyterian Medical Center (PMC), both located in Philadelphia, Pennsylvania. Light exposure was also measured for healthy non-hospitalized control subjects. In an attempt to evenly spread data collection of controls compared to subjects over the spring and summer, we collected three datasets from patients, and one from the control group per two weeks. ICU patients (or their health care proxy) and controls gave informed consent prior to participation, and received no compensation. The study was approved by the Institutional Review Board of the University of Pennsylvania.

The facility at HUP is a medical ICU with 12 acute care and 12 medium care beds. The facility at PMC is a mixed medical and surgical ICU with 15 acute care beds. All beds in both facilities are single-patient rooms enclosed by walls on three sides, that can be separated from the nurses' station by a sliding glass door on the remaining side. Artificial light sources in all ICU rooms, in both hospitals, consist of an overhead light at the patient's head and a ceiling light, a light for the patient, and light shining in from the adjacent nurses' station. The ICU rooms at HUP have either no window, or a window to the outside facing west with curtains and non-automatic outside shades. The ICU rooms at PMC involved in this study all have a window to the outside facing either east or west, also with curtains and non-automatic outside shades. The ICU at HUP is nine floors up and the ICU at PMC is two floors up (with approximately 10 feet between each floor).

Light levels were recorded continuously by means of an Actillume portable light meter (Ambulatory Monitoring, Inc., Ardsley, New York) programmed to store light level data at 1-minute intervals for a period of 48 hours beginning and ending at 14:00. The Actillume light meter was factory-calibrated to a Kodak Carousel 4200 Projector light source (300W).

For ICU patients, the light meter was placed at the head of the bed and affixed in such a way that it moved in the same plane as the patient's head. The distance

from the light meter to the patients' head was standardized and maintained at 3 to 6 inches, so as to accurately measure the light levels to which the patient's eyes were exposed. The direction the light meter faced was adjusted depending on the positioning of the patient's head, and checked hourly by the investigators. ICU patient care and routines were not altered, and nurses and healthcare providers were not informed of the purpose of the study. It is protocol in both ICU's to dim all light in the patient's rooms at 22:00, and turn them back between 6:30 and 7:30. All patients who were not expected to leave the ICU during the study-period were eligible for inclusion.

Non-hospitalized control subjects wore the light meter around the neck, over their clothing. At night the light meter was placed on the night stand next to the bed. Control subjects were encouraged to engage in their normal everyday activities. Control subjects were selected on having a regular 9-to-5 office jobs (which means they were indoors most of the time), who commuted to and from work in no more than 30 minutes, and did not participate in any outdoor activities after 22:00. Also, all control subjects worked in a radius of 2 miles from the hospitals.

By means of the ACTION3 computer program (Ambulatory Monitoring, Inc., Ardsley, New York), the light data (in lux) were averaged per hour and extracted for statistical analyses. As the human perception of light intensity is logarithmic, the hourly averages were ^{10}log transformed, yielding values in the range from –1 (equivalent to 0.1 lux or nearly pitch darkness) up to 5 (equivalent to 100,000 lux or bright sunlight). The hourly values of each individual's light level time series were labeled by the start times of the original 1-hour averaging intervals (i.e., 14:00 referred to light values observed from 14:00 until 14:59); in addition, the first 24 hours were marked "day 1" and the second 24 hours were marked "day 2". Subjects were categorized in four groups: patients in the ICU at the Hospital of the University of Pennsylvania (HUP) with a window to the outside in their room (n=10); patients in the ICU at HUP with no window (n=9); patients in the ICU at Presbyterian Medical Center (PMC) with a window (n=17); and healthy non-hospitalized controls (n=12).

Using the statistical software SPSS for Windows version 9.0.1 (SPSS Inc., Chicago, Illinois), the data were analyzed with repeated-measures analysis of variance (ANOVA) in a 24 times by 2 days by 4 groups design. To evaluate 24-hour variations in light exposure, time effects and interactions were considered (F tests with Huynh-Feldt correction). In case of a significant time by group interaction, two-sided Dunnett's T^2 post-hoc tests were performed for each time of day.

The results of the repeated-measures ANOVA were examined to verify the absence of significant variations from day 1 to day 2. The 24-hour variation in light exposure across the 48-hour time series was then modeled with least-squares non-linear regression; the computer program NLREG version 3.5 (Phillip H. Sherrod, Brentwood, Tennessee) was used to fit a sinusoid with a period of 24 hours to each individual's 48-hour time series. Mesor (i.e., center value), amplitude (i.e.,

maximum value minus center value) and phase (i.e., clock time of the maximum value) were determined for each subject's fitted sinusoid, as illustrated in Figure 1.

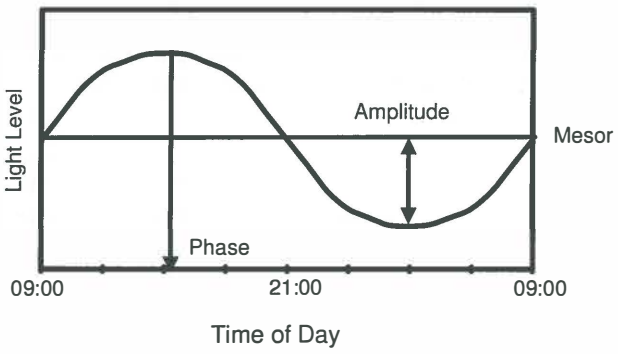


Figure 1: Schematic illustration of circadian mesor (center value), amplitude (maximum value minus center value), and phase (defined as clock time of the maximum) of a hypothetical sinusoidal 24-hour light pattern.

Contingent upon statistically significant goodness-of-fit for every subject, as verified with variance ratio F tests, the time series of all subjects were considered simultaneously to investigate differences among the four groups (HUP patients with a window, HUP patients without a window, PMC patients with a window, and controls). With the computer program NONMEM version V level 1.1 (GloboMax LLC, Hanover, Maryland), mixed-effects non-linear regression (32,33) was used to fit a sinusoid with a period of 24 hours to each group's combined data, while allowing for inter-individual differences in mesor, amplitude and phase via the inclusion of independent, normally distributed random effects. Planned contrasts were employed to compare the model parameters among the different groups. The statistical significance of the group differences was tested with Wald Z statistics.

For all ICU patients, Acute Physiology And Chronic Health Evaluation III (APACHE III) (34) scores were assessed. We correlated the mesor, amplitude and phase derived from each individual subject's fitted sinusoid with the APACHE III scores (ICU patients only), to assess any association of light exposure patterns with severity of illness. Correlations were determined using Pearson's r, and also with partial correlations controlling for group.

RESULTS

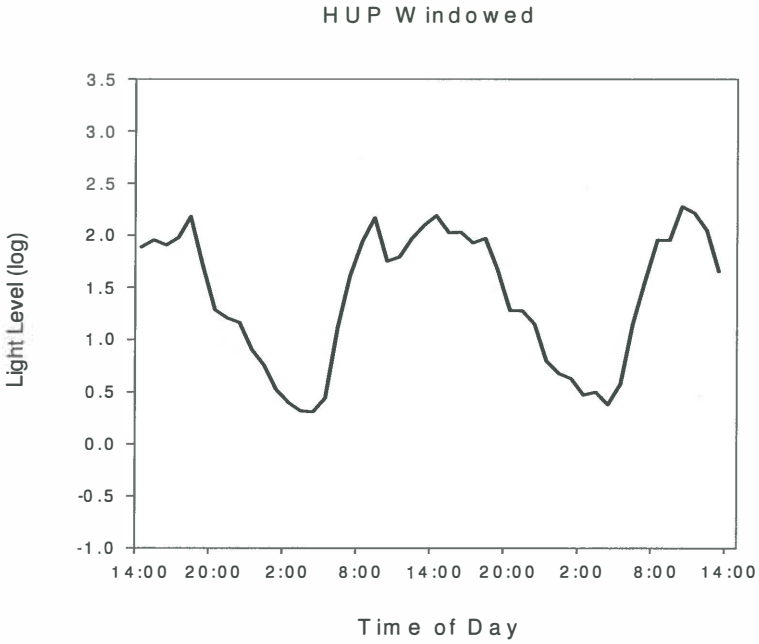
Light exposure was measured every week during weekdays in the period between March and September (except for one week in June) in the ICU at the Hospital of the University of Pennsylvania (HUP) and in the ICU at Presbyterian Medical

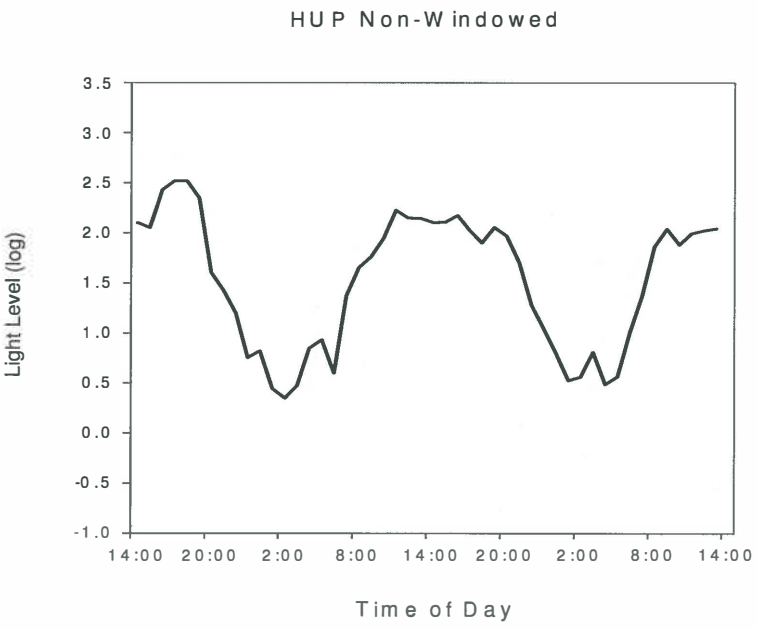
Center (PMC), both located in Philadelphia, Pennsylvania. Patients in the ICU at HUP had either a window to the outside facing west (group 1, n=10, age 52 ± 9, five males) or no window (group 2, n=9, age 56 ± 7, eight males). Patients in the ICU at PMC (group 3, n=17, age 57 ± 7, ten males) had a window to the outside facing either east (8 subjects) or west (9 subject). Healthy non-hospitalized controls (group 4, n=12, age 37 ± 12, nine males) lived and worked in the Philadelphia area. See Table 1 for demographics of the subject population.

	HUP (window)	HUP (no window)	PMC (window)	Controls
number of subjects	10	9	17	12
age (mean ± SD)	52 ± 9	56 ± 7	57 ± 7	37 ± 12
male vs. female	5 vs. 5	8 vs. 1	10 vs. 7	9 vs. 3
APACHE III (mean ± SD)	42 ± 13	50 ± 9	54 ± 20	
mechanically ventilated	8	7	14	
diagnoses: sepsis	3	3	5	
pneumonia	3	2	9	
COPD exacerbation	2	3	2	
ARDS	1	1	0	
myastenia gravis	1	0	1	
day of measurement relative to day of admission (mean ± SD)	9 ± 4	13 ± 6	11± 6	

Table 1: Demographics of study population.

Figure 2 shows the mean light exposure curves over 48 hours for each of the four groups. Repeated-measures ANOVA yielded a significant effect of time ($F_{23,1012}$=161.2, p<0.001) and a significant interaction of time by group ($F_{69,1012}$=18.2, p<0.001). Thus, there were pronounced 24-hour variations in light exposure, with substantial between-group differences in the 24-hour profiles. In particular, the healthy non-hospitalized control group was exposed to higher light levels during the day and lower light levels during the night than the ICU patients. Post-hoc tests revealed consistent (i.e., on both days 1 and 2) light level differences (significant at p<0.05) in the control group versus the ICU groups from 00:00 through 04:00 as well as at 15:00 (all ICU groups), at 16:00 and 17:00 (ICU patients with a window only), and at 05:00, 12:00, 13:00 and 18:00 (ICU at PMC only), with times of day indicating the start times of 1-hour bin averages. Overall, the difference between day and night was greater in the control group than in the ICU patient groups.


HUP Windowed
Light Level (log)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
14:00 20:00 2:00 8:00 14:00 20:00 2:00 8:00 14:00
Time of Day


HUP Non-Windowed
Light Level (log)
3.5
3.0
2.5
2.0
1.5
1.0
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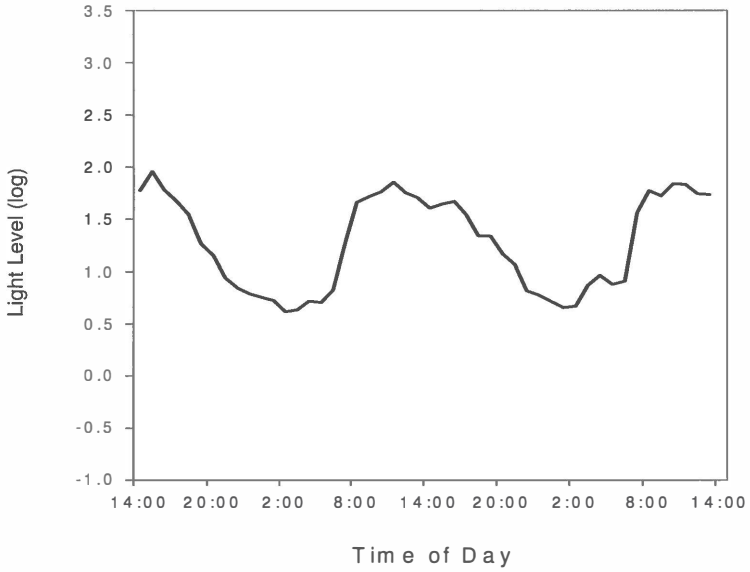
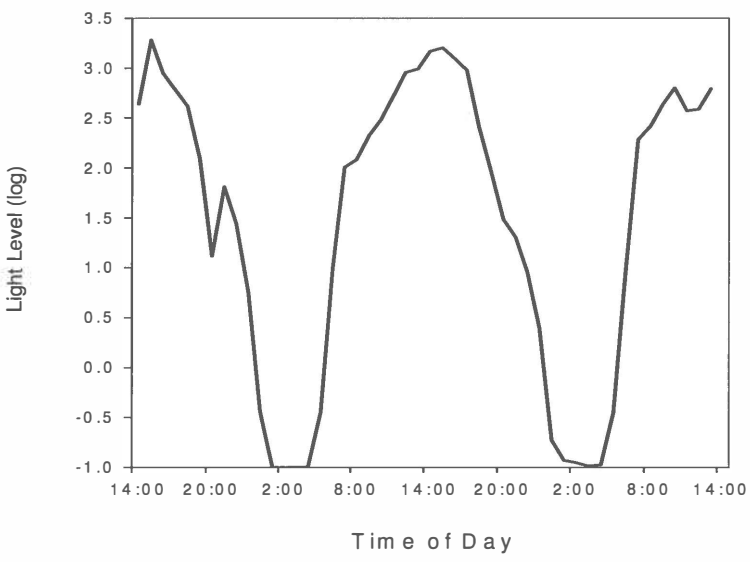
0.0
-0.5
-1.0
14:00 20:00 2:00 8:00 14:00 20:00 2:00 8:00 14:00
Time of Day

PMC



Non-Hospitalized Controls



There were no significant effects and interactions of day (i.e., no significant differences in light exposure patterns between days 1 and 2) in the repeated-measures ANOVA results. Just like the group average curves shown in Figure 2, individual subjects' time series were predominantly sinusoidal in shape. Analyses were therefore continued by fitting sinusoids with a 24-hour period to individuals' light intensity data. Goodness-of-fit of the sinusoid model was statistically significant ($p<0.005$) for every subject. The time series of all subjects could therefore be considered simultaneously using mixed-effects sinusoidal regression to compare the four groups (HUP patients with a window, HUP patients without a window, PMC patients with a window, and controls). Table 2 shows the means and standard errors for mesor (i.e., center value), amplitude (i.e., maximum value minus center value) and phase (i.e., clock time of the maximum value) of the sinusoids representing each of the four groups' light patterns.

Group	n	Phase (h clock time)	Mesor (^{10}log of lux)	Amplitude (^{10}log of lux)
HUP (window)	10	13.6 ± 0.4	1.42 ± 0.06	0.88 ± 0.09
HUP (no window)	9	14.6 ± 0.3	1.52 ± 0.09	0.91 ± 0.07
PMC (window)	17	12.9 ± 0.2	1.28 ± 0.05	0.60 ± 0.04
Controls	12	13.9 ± 0.2	1.48 ± 0.07	2.02 ± 0.07

Table 2: Group estimates ± standard errors of phase (as clock time for the maximum in hours), mesor (as log transform of lux value) and amplitude (as log transform of lux value) for sinusoids with a 24-hour period fitted to the 48-hour time series of light exposure using non-linear mixed-effects regression.

There were no statistically significant differences in the mesor of light exposure between the controls and any of the ICU patient groups ($|Z|<1.3$, $p\geq0.22$). The amplitude of 24-hour light variation was more than 50% smaller in each patient group relative to the non-hospitalized control group ($Z<-5.8$, $p<0.001$). No significant difference in phase was observed between the controls and the patients admitted at HUP ($|Z|<1.1$, $p\geq0.28$), but the patients admitted at PMC experienced the maximum of light exposure 1 hour earlier than the controls ($Z=-2.09$, $p=0.036$). The random effects for the model parameters, which were included in the mixed-effects regression to allow for inter-individual variability, showed that only relatively small inter-individual differences remained after the group differences were taken into account. For the mesor, the standard deviation (SD) for inter-individual variability was 0.21 log-transformed lux units (14% of the group mean for the controls); for the amplitude, the SD for inter-individual variability was 0.19 log-transformed lux units (9% of the group mean for the controls); and for the phase, the SD was 0.7 hours (approximately 3% of the 24-hour day). Taken together, these findings revealed that the difference in light levels between day and night was consistently greater in the control group than in the ICU patient groups.

There were no statistically significant differences in the mesor of light exposure among the three ICU patient groups ($|Z|<1.5$, $p \geq 0.20$). The amplitude of the 24-hour variation in light exposure was significantly smaller in the ICU patients at PMC than in both groups at HUP ($|Z|>2.0$, $p \leq 0.40$). No significant difference in amplitude was observed between patients at HUP with a window and patients at HUP with no window in their room ($Z=0.18$, $p=0.86$). There also was no significant difference in phase between these two patient groups ($Z=1.17$, $p=0.24$). Thus, the effect of having a window in the ICU room appeared to be negligible.

No statistically significant correlations were found between ICU patients' APACHE III score and the mesor, amplitude and phase of the sinusoid fitted to their light data ($|r|<0.1$, $p>0.59$). Partial correlations controlling for group also showed no significant associations between APACHE III score and light parameters ($|r|<0.2$, $p>0.29$).

DISCUSSION

We studied environmental light patterns in ICU patients of two different hospitals and in healthy non-hospitalized controls, to investigate if abnormal light exposure could be a cause of circadian rhythm disturbances in the ICU. Using a state-of-the-art statistical analysis technique (i.e., non-linear mixed-effects regression), we showed that ICU light–dark patterns were significantly different than the light exposure profile of the control subjects: In comparison to controls, ICU patients were exposed to significantly lower light levels during the day and relatively higher light levels during the night. Thus, although day–night variations in ICU light levels were present, and stable across the two days of the study period, the amplitude of the day–night variability in light exposure was smaller in ICU patients than in non-hospitalized controls. No significant correlations between severity of illness and light exposure parameters were found, suggesting that ICU patients may be at risk for abnormal light exposure regardless of clinical profile. The present results do not corroborate, however, the assumption that the ICU environment is one of constant lighting.

While stability of light patterns across days was high in the present data, it should be recognized that the study period was only 48 hours. It is possible that longer observation periods would have demonstrated significant day-to-day (e.g., seasonal) variations in light exposure. Interestingly, we observed no significant difference in light patterns between patients whose rooms had windows and patients whose rooms had no windows. Why light exposure was similar with or without window to the outside remains to be investigated. The finding may be related to an increased need to use artificial light for patient care during the day in rooms without a window. In addition, we have anecdotal evidence from interviews with the nursing staff that the non-automatic blinds and drapes were frequently drawn in windowed rooms.

The present results may not be generalizable to all types of ICU patients and settings, since the study assessed light–dark exposure predominantly in mechanically ventilated ICU patients, in single-patient closed rooms in a tertiary care urban setting. APACHE III score were the only factor we used to differentiate patients with regard to severity of illness. Our study sample did encompass patients with surgical, medical and cardiac problems, similar to the samples of most studies that objectively assessed circadian rhythm abnormalities in ICU patients (4-7,22,24). There were significant differences in the ages of the ICU patients versus the healthy non-hospitalized controls, with the control subjects being significantly younger. There is no reason to believe that this age difference affected the study findings, since measurements were taken from the environment, not from subjects' endogenous neurobiology.

The photoreceptors involved in circadian entrainment reside within the retina (35). Therefore, light's ability to synchronize and/or change circadian rhythms is dependent on ocular exposure. In the only previous study of light in the ICU, Meyer et al. (31) measured room light without regard to the position of the patients' eyes, with the light meter positioned between the patients' bed and window. In the current study, light meters were positioned in such a way as to measure the light levels to which the patient's eyes were exposed. We could not, however, take into account eyelid closure. Thus, the present study only showed that light patterns are a possible cause for circadian rhythm disturbances in ICU patients—causality remains to be determined.

Low light levels like those observed in the ICU in our study could have the ability to normally entrain circadian rhythms (30) if patients would remain awake with eyes open during the day and sleep with their eyes closed at night. Previous ICU studies have demonstrated that this is typically not the case (4-7,22,24). Most patients sleep intermittently throughout the day and night, with loss of the uniphasic circadian distribution of sleep typically seen in healthy individuals. Also, ICU patients may be heavily sedated, having their eyes closed for many days. Thus, it is unclear if the relatively low light levels observed in our study could effectively entrain the circadian rhythmicity of patients, given the intermittent nature of retinal exposure to light likely to occur in this population. In this context, sedation may not be an unambiguously advantageous component of recovery treatment for ICU patients, as it may interfere with the ability to entrain circadian rhythms by light because of eye closure.

Mounting evidence shows that ICU patients have abnormal circadian rhythms, as observed in altered sleep–wake, melatonin secretion and core body temperature cycles (4-7,10,11,23). In another study (8,23), we measured core body temperature, a traditional physiologic marker of circadian rhythmicity, in a group of 21 ICU patients. The circadian phase position for 17 of these patients fell outside the normative range for variability among healthy normal adults. Altered light--dark patterns in the ICU may have contributed to these circadian abnormalities. Recent observations that even low-level light can be sufficient to affect the circadian

pacemaker (28,30) would suggest that during the night, light exposure in the ICU—which was found to be more intense at night than in normal controls—may be sufficient to adversely influence circadian rhythmicity. Computer simulations with biomathematical models of the circadian pacemaker (36,37) may be useful to investigate this issue more precisely.

CONCLUSIONS

In conclusion, our findings revealed light to be a potential source for the disruption of circadian rhythmicity in ICU patients, as light levels in the ICU were different than what normal controls were exposed to. Further research is needed to assess the countermeasure potential of carefully timed and appropriately dosed light to maintain or restore circadian rhythmicity. Training ICU personnel in the management of environmental light may be a valuable first step towards improving circadian rhythms in ICU patients.

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Chapter 5

The Effect of Overnight Sedation on the Sleep/Wake Cycle in the Intensive Care Unit

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Intensive Care Unit (ICU) patients have been documented to exhibit abnormal sleep/wake cycles. It has been suggested that normal night/day sleep/wake cycles can be restored by overnight sedation. This study evaluated the effect of overnight sedation on daytime sleep/wake behavior in ICU patients using a within-subject study design. Continuous polysomnography recordings where performed for 72 hours in n=15 ICU patients (mean age 62 ± 8 yrs). The first 24 hours of recording were considered the baseline. The second and third 24-hour periods involved continuous propofol 2% infusion between 22:00 and 6:00, aiming at sedation level of a Ramsay 3 score. Total sleep time (TST) in the baseline period was 7.3 ± 3.0 h, and 51% of this sleep occurred during the daytime hours. TST during the daytime hours of the first and second intervention days showed no significant changes compared to baseline. There were no significant correlations of TST and time in the different sleep stages versus age, duration of ICU stay, or APACHE III score. While overnight sedation may result in a behavioral state resembling sleep during the night, it appears not to be a good strategy for restoring a normal night/day sleep/wake cycle in ICU patients.

Most human physiologic processes exhibit circadian (i.e., near-24-hour) rhythms, of which the most easily observed expression in healthy subjects is the daily alternation of wakefulness and sleep. Evidence suggests that intensive care unit (ICU) patients have disturbed circadian rhythmicity, reflected for instance in abnormal sleep/wake patterns and disrupted sleep architecture [1-7]. In a recent study [8], we observed sleep in ICU patients to be fragmented and non-consolidated, with 57% and 43% of the total sleep time occurring during the day and night respectively. Even though the total sleep time (TST) per 24 hours is comparable to the amount typically observed in healthy subjects, ICU patients tend to sleep more during the day and less during the night [3;8].

The potential physiologic ramifications of these altered sleep/wake patterns have been widely discussed in the literature [9]. Sleep deprivation and sleep fragmentation have been shown to adversely affect respiratory muscle performance in healthy subjects [10-12]. Also, sleep fragmentation as seen in patients with sleep apnea may result in elevation of arterial blood pressure, elevation of serum catecholamines, cardiac arrhythmias, and progressive cardiac failure [13;14]. Sleep deprivation may also contribute to delirium, agitation [15;16]and unfavorably altered immune function [17-23]. Altered sleep/wake patterns in ICU patients may therefore have important implications for health care in the ICU.

Recognizing the importance of normal sleep/wake cycles in ICU patients, investigators have studied the efficacy of (additional) overnight sedation for restoring and maintaining normal sleep/wake cycles [24-26]. These studies suggested that sleep quality, measured through a self-assessment scale (Hospital Anxiety and Depression Scale) and sedation scores (Ramsay scores) may improve during the next day after overnight sedation, although statistical significance was not reached [24-26]. None of these studies used continuous polysomnography to

precisely assess 24-hour sleep patterns, however, so that the question whether normal night/day sleep/wake cycles can be restored by overnight sedation has remained unanswered [9].

The present study was designed to objectively evaluate the effects of short-term overnight sedation on daytime sleep using continuous polysomnography in ICU patients. Our goal was to determine if overnight sedation restored normal sleep/wake patterns in ICU patients.

METHODS

This study was performed, after being approved by the Medical Ethical Committee, at the University Medical Center Groningen in the Netherlands of the University of Groningen.

SUBJECTS

ICU patients who were expected to remain in the ICU for a period of 72 hours were eligible for participation. Patients were excluded if they, prior to the initiation of the study, were stuporous or comatose, exhibited or were suspected of sepsis, had a history of epilepsy, dementia, and/or were receiving continuous heavy sedation. Heavy sedation, defined by inability to arouse the patient or the patient's inability to follow verbal commands, was a criterion for exclusion because we could not reliably distinguish sleep from wakefulness in heavily sedated subjects. Patients with a history of dementia were excluded because of the abnormal EEG patterns in demented patients which make it difficult to accurately distinguish sleep from wakefulness by EEG criteria [27]. Patients with (suspected) sepsis where also excluded, as recent studies found these patients to have an unscorable EEG for sleep detection purposes [3;4]. For each patient, an Acute Physiology, Age and Chronic Health Evaluation (APACHE III) score was calculated at the onset of the investigation [28]. Patients or their legal representatives gave written consent prior to study participation and received no compensation.

POWER CALCULATION

The number of subjects studied in this investigation was determined a priori by means of a statistical power calculation. Recently published data was used to determine the sample size for this investigation. Cooper et al measured the amount of baseline daytime sleep in ICU patients, and showed in 20 critically ill patients (12 males, 8 females, age 62 ± 15 years), that daytime (06:00–22:00) sleep was 240 ± 174 minutes (57% of the total sleep time). The null hypothesis for the present study was that sedation would have no effect, so that daytime sleep after overnight sedation would be equal in duration to baseline, with an expected value of 240 ± 174 minutes. We contrasted this with the alternative hypothesis that daytime sleep after nighttime sedation would be less than the criterion of 78 minutes, reported for narcolepsy, the pathological daytime sleep [29]. Testing the null hypothesis against

the alternative hypothesis with a one-sided paired t-test, this would constitute an effect size of 0.93. It followed that, in order to achieve 95% power (i.e., to cap type II error at 0.05), n=15 subjects would be needed for our study [30].

We also assessed how much statistical power there would be for testing the alternative hypothesis in case the null hypothesis would not be rejected. The standard deviation for the average of 78 minutes in Volk et al. (1990) was derived from the range reported in that paper (22.5–144.5 minutes), and estimated to be 46 minutes [30]. Testing the alternative hypothesis with a one-sided one-sample t-test constituted an effect size of 3.50. It followed that with n=15 subjects, more than 99% power would be achieved for testing the alternative hypothesis.

Sedative of Choice

Patients admitted to the ICU may require sedation to minimize distress due to pain, discomfort and anxiety, to facilitate mechanical ventilation, nursing interventions and promote amnesia. Benzodiazepines, narcotic analgesics, and propofol are the most commonly used agents sedatives [31]. The ideal sedative would have a rapid onset of action with rapid recovery, it would lack the problem of drug accumulation, would be easy to titrate to varying levels of sedation, exhibit no tachyphylaxis or withdrawal symptoms, cause no haemodynamic instability and be inexpensive [31-33]. It is clear that benzodiazepines, narcotic analgesics nor propofol, although being the most commonly used agents in the ICU, have any of these properties as a single drug [32]. We chose to use propofol because it has a documented rapid on- and of-set from its sedative effect [34-36]. Our research design required patients to reach a Ramsay score of 3 within 30 minutes after the start of drug infusion. It also required patient to be fully awake within 30 minutes after terminating sedative infusion. A recent study of propofol, with EEG monitoring before, during and after sedation (at a Ramsay score of 3), showed that EEG patterns returned to normal about 20 minutes after ending the infusion [37].

Sedation Protocol

The study period of 72 hours was divided in 3 blocks of 24 hours each. The first 24 hours of recording (which started at 22:00), during which no interventions where made, served as the patients baseline. At 22:00, the onset of the second 24-hour block, propofol 2% (Diprivan®, Astra-Zeneca) infusion was initiated at a rate of 1.0 mg/kg/h, as recommended by previous investigators [36;38], and adjusted upwards with small increments (0.5 mg/kg/h) at intervals of 5 minutes until the desired Ramsay score [39] of 3–4 was reached (see table 1). The sedation level was re-evaluated at 02:00 and 04:00, and infusion rates increased if the targeted Ramsey score was not reached. The propofol 2% infusion was stopped at 06:00. At 06:30, a Ramsay score was calculated to assure the patient was fully awake. This overnight sedation routine was repeated for the third 24-hour block, except that the infusion was initiated at a rate 0.5 mg/kg/h lower than the average rate of the night before, in order to reach our target sedation level faster.

Sedation score	Level of sedation
1	Anxious and agitated or restless
2	Cooperative, oriented and tranquil
3	Responds to commands only
4	Brisk response to light glabellar tap
5	Sluggish response to light glabellar tap
6	No response to light glabellar tap

Table 1: Ramsey Sedation scale

POLYSOMNOGRAPHY

All subjects were monitored continuously for 72 hours with standard polysomnography using a portable polysomnograph (Biologic, Mundelein, IL). Electrode leads were placed on the patient's scalp in the C3, C4, and Oz positions, and referenced to electrode leads placed at A1 and A2, according to the International 10/20 system of electrode placement. Two electro-oculogram (EOG) leads and two submental electromyogram (EMG) leads were applied to assess ocular movements and muscle tone, respectively, in order to differentiate REM sleep from non-REM sleep and wakefulness. The polysomnographic records were scored according to the criteria of Rechtschaffen and Kales [40] by qualified neurophysiologists who were kept unaware of the purpose of the study. The following sleep variables were derived: 24-hour total sleep time (TST), daytime sleep (total time and percentage of total sleep time), 24-hour as well as daytime duration of each of the sleep stages (1, 2, 3 and 4 combined, and REM), the amount of sleep bouts and their duration.

STATISTICAL ANALYSIS

For each patient, daytime (06:30–22:00) sleep variables were assessed as outlined above. Per patient, this resulted in three values for each variable: one for the baseline day, and one for each of the intervention days. The sleep variables for the first intervention day were compared to those from the second intervention day by means of paired t-tests. In the absence of significant differences, the results of the first and second intervention days were averaged within subjects to reduce noise in the data; otherwise, only the results of the second day were used for primary analyses. The outcomes for the intervention period were then compared with the sleep parameters for the baseline day. The null hypothesis of no difference between baseline and intervention was tested against the alternative hypothesis of

less daytime sleep following sedation compared to baseline, by means of one-sided paired t-tests.

The comparison between the baseline period and the intervention period for total sleep time (TST) constituted the key analysis for this study, as it established whether overnight sedation was successful in reducing daytime sleep in ICU patients (potentially leading to normalization of the sleep/wake cycle). We also planned to investigate whether daytime sleep amounts following the intervention fell below a lower limit of pathological daytime sleep reported in the literature. We used the average of 78 minutes reported for narcolepsy [29], and planned to employ a one-sided one-sample t-test to compare daytime TST observed after overnight sedation to this criterion.

Pearson's correlation analysis and one-way analysis of variance (ANOVA) were used to determine the relationship of patient age, duration of ICU stay, and APACHE III score with each of the sleep variables at baseline.

RESULTS

DEMOGRAPHICS

In order to obtain the target population size of n=15, 17 surgical ICU patients were enrolled between September 2000 and July 2002. Two patients where excluded after enrollment because of suspected sepsis (tachycardia, fever, hypotension). The study population was comprised of 8 males and 7 females aged 62 ± 8 years (range 50–79), with APACHE III scores of 57 ± 22 (range 29–90). Their duration of stay in the ICU prior to participation in the study was 22 ± 9 days (range 10–38). All patients had undergone abdominal surgery, and were mechanically ventilated at the time of the experiment, and remained mechanically ventilated for the entire study period. None of the patients received sedation during the study period other than the propofol 2% on the two intervention days. Five patients received intravenous low doses of fentanyl (maximum of 2 ml/hr of pure fentanyl). No patients were on tricyclic or other types of anti-depressant medications during the study period.

SEDATION LEVELS

On the first sedation night, two patients needed an additional five minutes (i.e. 35 instead of 30 minutes of titration) to reach a Ramsay 3 score. All others obtained a Ramsey score of 3 at 22:30. The average infusion rate was 2.9 ± 0.6 mg/kg/hr. Two patients required an increase of 0.5 mg/kg/hr during the night to remain sedated at a Ramsay score of 3.. During the second infusion night, all patients showed a Ramsay 3 score at 22:30. The average infusion rate being 3.0 ± 0.4 mg/kg/hr. One patient required an increase in infusion rate of 0.5 mg/kg/hr during the night to remain sedated at a Ramsay score of 3.

SLEEP DISTRIBUTION

All 15 patients had a sleep scorable EEG according to the criteria of Rechtschaffen and Kales [40]. Table 2 shows the TST, sleep stages, number of sleep bouts, and average sleep bout duration during the 24-hour baseline day and the daytime periods following the first and second overnight sedation intervention periods. The 24-hour baseline period had a mean TST of 7.3 ± 3.0 h (mean ± s.d.), with large inter-individual differences in the baseline TST, ranging from 3.1 h to 12.2 h. Almost 51% of the total sleep time occurred during the day (6:30-22:00); 3.4 ± 1.5 h (mean ± s.d.). The TST was distributed over 35.1 ± 23.2 (mean ± s.d.) sleep bouts with a mean duration of 17.8 ± 10.8 (mean ± s.d.) minutes.

	Baseline 24 h	Baseline day	Intervention day 1	Intervention day 2
TST (h)	7.3 ± 3.0	3.4 ± 1.5	3.6 ± 1.2	3.2 ± 1.3
% stage 1	57.3 ± 21.2	57.5 ± 20.1	55.2 ± 16.8	55.5 ± 18.4
(min ± SD)	(260 ± 148)	(122 ± 72)	(118 ± 52)	(105 ± 50)
% stage 2	27.9 ± 12.2	27.8 ± 11.9	32.7 ± 11.5	30.1 ± 14.9
(min ± SD)	(119 ± 57)	(57 ± 31)	(70 ± 30)	(57 ± 40)
% stage 3/4	8.9 ± 5.5	9.3 ± 6.6	6.8 ± 6.7	8.1 ± 6.7
(min ± SD)	(39 ± 27)	(18 ± 13)	(16 ± 16)	(17 ± 16)
% REM	5.9 ± 7.0	5.5 ± 6.7	5.3 ± 7.0	6.4 ± 7.1
(min ± SD)	(20 ± 24)	(9 ± 11)	(11 ± 14)	(10 ± 10)
# sleep bouts	35.1 ± 23.2	18.1 ± 14.3	14.9 ± 12.7	9.5 ± 6.8
Sleep bout duration (min)	17.8 ± 10.8	20.6 ± 16.9	34 ± 40.1	28.6 ± 21.9

Table 2: Total sleep time (TST), sleep stages (both in minutes and as % of TST), number of sleep bouts, and average sleep bout duration, during the 24-hour baseline day as well as specifically during the baseline daytime period (06:30–22:00), and during the daytime (06:30–22:00) periods following the first and second overnight sedation interventions.

The mean daytime TST from the first intervention day (3.6 ± 1.2 h {mean ± s.d.}) were compared to the mean daytime TST from the second intervention day (3.2 ± 1.3 h {mean ± s.d.}) by means of paired t-tests, showing no significant changes ($p=0.109$). In the absence of significant differences, the results of the first and second day were averaged within subjects. Comparing the average daytime TST for the sedation days with the TST for the baseline day by means of one-sided paired t-tests showed no statistical significance ($p=0.781$). A one-sided one-sample t-test comparing daytime TST observed after overnight sedation to our 78-minute lower limit did not yield statistical significance ($p<0.001$). Thus, the overnight sedation strategy was not successful in restoring a normal night/day sleep/wake cycle. There was no significant correlation ($p=0.381$) between TST and age, duration of ICU stay, or APACHE III score.

SLEEP STAGES

There was a predominance of stage 1 sleep (mean ± s.d. 57.3 ± 21.2 %); and decreased amounts of stage 2 sleep (mean ± s.d. 27.9 ± 12.2 %), slow-wave sleep (mean ± s.d. 8.9 ± 5.5 %) and REM sleep (5.9 ± 7.0 %) in the 24-hour baseline PSG. REM sleep did not occur in eight patients (i.e., more than 50% of the population).

There were no significant differences (p=0.265) between the baseline day and the average of intervention days 1 and 2 with respect to mean total time spent in any of the sleep stages, nor any significant correlations (p=0.283) between time in any sleep stage and age, duration of ICU stay, or APACHE III score.

DISCUSSION

This is the first continuous polysomnographic study systemically evaluating the effectiveness of overnight sedation for restoring a normal night/day sleep/wake cycle in ICU patients. Our patient sample experienced the characteristic sleep disturbances during their baseline recording, described in previous investigations [1-4]: They tended to sleep in short, non-consolidated periods, abnormally distributed over the 24-hr baseline period, with a predominance of stage 1 sleep and decreased stages 2, 3, 4 and REM sleep. More than 50% of the patients did not even go through REM sleep at all, analogous to studies by Cooper at al. (2000) and Freedman et al (2001) [3;4]. Overnight sedation did not result in less sleep occurring during the following day. Patients continued to sleep excessively during the daytime (6:30 – 22:00) after overnight sedation. Also, there were no significant differences in sleep stages between the baseline day and the overnight sedation intervention days.

RESEARCH CONSIDERATIONS

There are several research limitations to the scope of our findings. Our results may not be generalizable to all ICU patient populations as the majority of the patients that we evaluated were non-sedated mechanically ventilated ICU patients. However, this is a very important patient population since many ICU patients are mechanically ventilated. Our results may not be applicable to other sedatives like benzodiazepines. There may have also been a selection bias as the patients that were selected to participate based on their likelihood of remaining in the ICU for a continuous 72 hr period and were therefore not randomly selected. We only investigated the short-term effect of sedation over a period of 48 hr, we did not examine the effect of longterm overnight sedation. We did not control for the length of stay in the ICU. However, the abnormalities and the lack of effect of overnight sedation were evident regardless of the length of stay. Also, the absence of significant differences in total sleep time and time in various sleep stages between any of the studied days, even after overnight sedation, suggests that there is little day-to-day variation in sleep architecture. Our findings do not confirm

the suggestions made by previous investigators that overnight sedation can restore abnormal sleep/wake cycles in ICU patients [24-26].

COMPLICATIONS OF SEDATION IN THE ICU

Using sedatives in order to restore the sleep/wake cycle in ICU patients is not entirely without risk. Sedation of ICU patients could be optimized if the pharmacokinetic and pharmacodynamic profiles of the various drugs were well understood and described. However, critically ill patients frequently exhibit unpredictable alterations in pharmacokinetic and pharmacodynamic profiles. Drug-drug interactions, renal and hepatic dysfunction, impaired gastrointestinal absorption and circulatory instability add to the unpredictability of sedative use in the ICU. The most common complication is drug accumulation, which has been reported to lead to prolonged duration of mechanical ventilation by 2.5 days and prolonged ICU stay by 3.5 days [41]. Prolonged hospital stays, increased utilization of diagnostic procedures and imaging modalities to adequate monitor a patients neurological functions have also been reported as frequent complications of "oversedation"[31; 32; 42; 43] Also, patients receiving prolonged infusion of sedatives may experience withdrawal symptoms, regardless of age ([32;44-46]. Cammarano et al (1998) found a 32% incidence of withdrawal in adults receiving opioid and benzodiazepine infusion [45]. Finally, a complication of deep sedation is its ability to mask development of intracranial, intrathoracic, or intra-abdominal catastrophes. The sedation period of the current study may haven been too short to cause any of these complications. However, caution in administering and careful titration of sedatives to critically ill patients is still prudent.

SLEEP PROMOTING MEASURES

Another, non-pharmacological, way of restoring or maintaining sleep/wake cycles in ICU patients is by understanding the mechanisms responsible for disrupting the sleep/wake cycles in ICU patients, and subsequently preventing them from taking place. The etiologies of the sleep disturbances in the ICU, as reported in this study, are presumed to be multifactorial [3;4;9]. A combination of environmental stimuli [3;4;47-53], circadian abnormalities [54-58] and the underlying disease [1;2;4;7;55;59]are most likely to be responsible for disrupting sleep in the ICU.

From all environmental stimuli, noise has been singled out as a major sleep disruptive factor and reaches levels substantially higher than recommended by the Environmental Protection Agency for maximum hospital noise levels, both during the day and during the night [4;9;48;50;52;60]. Noise levels reported in literature range from 50 to 75 dB, with peaks up to 85 dB[3-5;48-51;53;61]. These noise levels are comparable to that of a factory (80 dB) or a busy office (70 dB) and have objectively demonstrated to be responsible for at least 17% of the awakenings from sleep [3;4]. From the standpoint of the ICU environment, other factors, like the ICU lighting [62], the patients pain/anxiety/discomfort [63], and underlying disease [1;2;4;7;55;59] also have a disturbing influence on the sleep/wake cycle.

Understanding and controlling these factors may improve sleep/wake cycles better than overnight sedation of ICU patients.

The occurrence, duration and structure of sleep are modulated by circadian (i.e., near-24-hour) rhythmicity, that is, by the biological clock in the suprachiasmatic nuclei of the hypothalamus [64]. Time cues such as the light-dark cycle synchronize (i.e., "entrain") circadian rhythms in the healthy human body to the environment [65]. In ICU patients, there is strong evidence that circadian rhythmicity is disturbed [54-58]. While the evidence of abnormal circadian rhythmicity in the ICU is mounting, no single study has yet investigated the extent to which these are linked with sleep disturbances in ICU patients. However, understanding the (abnormal) circadian rhythmicity in ICU patients, and the ability to restore it, could be of great importance with respect to the sleep/wake cycle of ICU patients because of its major regulatory effect on sleep.

CONCLUSIONS

In conclusion, our findings revealed that ICU sleep/wake abnormalities were not restored by overnight sedation. The use of sedatives in the ICU may be essential for many reasons, such as increased patient comfort, decreased anxiety and agitation, but not for managing sleep. Establishing the cause of the sleep/wake disorders, whether they are caused by environmental factors or disturbed circadian rhythmicity, and controlling them, may prove to be more effective in maintaining or restoring sleep/wake cycles in the ICU.

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Chapter 6

BBC improves Circadian Rhythm in the Intensive Care Unit

Good sleep and normal circadian rhythms, essential physiological needs, are difficult to achieve in the intensive care unit (ICU). Studies have suggested this is caused by a lack of synchronization of the biological clock due to the absence of proper time cues in the ICU environment. For a period of 9 days, core body temperature (as a measure of circadian rhythmicity) and a modified mini-mental-state-exam where recorded in one of our ICU patients (female, 67 yrs), whose circadian rhythms were initially severely disrupted. The patient's only reliable source of time information was the television, tuned to the British Broadcasting Company (BBC). During the recording period, her circadian rhythms and mental capacity improved significantly. This case study suggests that normal circadian rhythms maybe restored in the ICU by a single effective time source, and indicates that improvement of circadian rhythmicity may be associated with positive clinical outcome.

Good sleep and normal circadian rhythms (i.e., near-24-hour) are essential physiological needs and believed to be important mediators of recovery from clinical events. In the intensive care unit (ICU), however, patients tend to develop abnormal sleep-wake patterns and altered circadian rhythmicity [1]. There is evidence this is caused by lack of entrainment (i.e. synchronization) of the biological clock – the circadian pacemaker in the suprachiasmatic nuclei (SNC) of the hypothalamus – due to absence of proper time cues (e.g., normal light-dark cycles) in the ICU environment [2]. Altered circadian rhythms have been shown to reduce the effectiveness of critical functions (e.g., respiration), and to affect the efficacy, half-life and toxicity of medications[3,4]. This has substantial implications for ICU patients – achieving normal circadian rhythms and sleep in the ICU may be associated with improved outcome. Here we report on a severely ill ICU patient whose circadian rhythmicity, as measured by core body temperature (CBT), surprised us by synchronizing to an unexpected time source.

Our patient, a 67 year old lady from Scottish descend, was admitted to our surgical ICU in a severe septic state. She was diagnosed with a leaking anastomosis after a sigmoid resection, developing additional complications including: ARDS (acute respiratory distress syndrome), abdominal abscesses and fistula and renal insufficiency. She stayed in our ICU for a total period of 42 days, of which the first 21 days where under strong inotropic (nor-epinephrine) and antibiotic support. She was intubated at admission, and changed to a tracheotomy after 18 days.

The patient's weaning process was initiated 20 days before her release, and completed 9 days before she was released to the general ward. At this time (9 days prior to discharge from the ICU), we began continuous recording of CBT using a temperature-sensing rectal probe (Mallinckrodt, Inc., St. Louis, MO), in order to measure circadian rhythmicity. During the 9 days of CBT recordings, the patient did not receive any inotropic support, sedation, steroids or antibiotics. She was continuously tube fed until discharge. She resided in a private non-windowed room, with light-levels below 180 lux at all times. She received one 30-minute visit every other day between 14:00 and 17:00. Every day at 16:00 a modified mini-

mental-state-exam (MMMSE) was taken. A television, placed next to her bed, was tuned to the British Broadcasting Company (BBC) from 8:00 until midnight.

Figure 1 shows the CBT observations over the 9 days of recording. For each of these days, a sinusoid with a period of 24 hours was fitted to the CBT data to quantify the circadian rhythm. Goodness-of-fit (as evaluated by explained variance) improved steadily from R^2=3.4% on day 1 to R^2=93.1% on day 9, and estimated rhythm amplitude (± standard error) increased from 0.04 ± 0.01 ºC on day 1 to 0.66 ± 0.01 ºC on day 9. Linear regression showed a significant increase of the amplitude of circadian rhythmicity over the 9 days (t_7=4.11, p<0.0045). Thus the CBT profile became progressively more similar to a robust 24 hours sinusoid with an amplitude of approximately 0.5ºC, which is the profile typically observed in healthy individuals under standardized conditions of bed rest. The body temperature minimum, a marker of circadian phase, moved from 12:00 ± 132.0 min (estimate ± standard error) on day 1, to 05:51 ± 3.7 min on day 9. The latter phase position is well within the boundaries of circadian phase for healthy adults (04:38–06:45) [5]. The patient's score on the MMMSE, which could range from 0 to 15, improved from 0 on the day following the completion of weaning (day 1) to 14 on the day of discharge (day 9). Linear regression showed that her MMMSE scores improved significantly (t_7=8.45, p<0.0001).

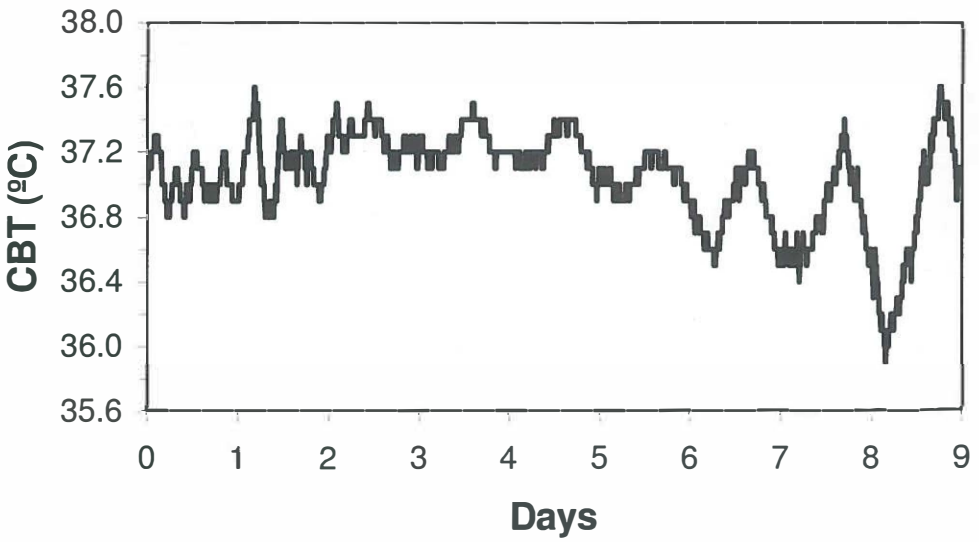

Figure 1: Core body temperature (CBT) measurements (in ºC) over the last 9 days of this patient's stay in the ICU. The data clearly show the recovery of circadian rhythmicity, from an erratic pattern on the day after weaning to a robust rhythm on the day of discharge.

Our patient had been severely ill, was tube fed, did not engage in any physical activity, and resided in a dimly lit room with no significant fluctuations in ambient temperature or other environmental factors. Nevertheless, the patient's severely disrupted circadian rhythms were restored and properly entrained in the period from completion of weaning until discharge. In conjunction, she improved markedly in mental capacity. To our knowledge, her only source of time information has been the television placed by the side of her bed.

This case study illustrates that normal circadian rhythmicity can be restored in the ICU, and that a single effective time source may suffice to achieve this. Furthermore, the results indicate that normal circadian rhythms ma be associated with positive clinical outcome. It would appear that the BBC deserves credit for the recovery of this ICU patient.

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Chapter 7

SUMMARY

The main goal of this dissertation was to gain more insight into the sleep-wake behavior of intensive care unit patients and the factors that disturb it. At the beginning of this project, we firmly believed that patients experienced abnormal sleep-wake behavior. This was based on clinical observations and several (subjective) publications.

Chapter 1 offers an introduction to sleep (research) in the ICU. It illustrates how little was known about sleep-wake patterns in the ICU prior to our first investigation in 1999 and about the mechanisms responsible for abnormalities in these patterns. Most assumptions regarding sleep and its disruptions were based on common sense, rather than objective evaluations. Sleep in ICU patients had only been examined in small populations, mainly during nocturnal hours. All of the investigators agreed, after employing subjective research methods, that ICU patients are sleep deprived. Environmental stimuli were singled out as the most disruptive factors, with noise as the worst of these. ICUs tend to be noisy around the clock, preventing patients from achieving a normal day/night sleep-wake pattern. The effects of sleep deprivation have been investigated primarily in animal models, where impaired psychological and physiological functioning have been shown to develop. In the few studies conducted using human subjects, it has been suggested that sleep deprivation may lead to the ICU syndrome. Finally, this chapter postulates several measures to promote sleep.

Chapter 2 evaluates the effect of environmental noise on sleep disruptions in the ICU. This investigation was the first to directly link the measurement of environmental noise levels with continuous polysomnography, the golden standard in sleep research. All the patients evaluated showed sleep-wake cycle abnormalities. In sharp contrast to previous literature, this study demonstrated that ICU patients were on average not sleep-deprived; their total sleep time per 24 hours was comparable to healthy subjects who sleep a mean of 8.8 hours per 24-hour period. What we found was that ICU patients tend to distribute their sleep evenly over day and night, with more than 50% of the total sleep time occurring during the daytime hours. Also, environmental noise was found to not be as important with regard to sleep disruptions as was previously presumed. Environmental noise was responsible for 11.5% and 17% of the overall arousals and awakenings from sleep, respectively. This investigation also proved that 24-hour recordings of sleep times using polysomnography are essential to reliably evaluate sleep in the ICU.

Chapter 3 addresses the altered circadian rhythmicity in ICU patients. The occurrence, duration and structure of sleep are modulated by circadian (i.e., near-24-hour) rhythmicity, that is, by the biological clock in the suprachiasmatic nuclei of the hypothalamus. Our previous study proved not only that sleep-wake cycles in the ICU are abnormal, but also that the cause of these abnormalities may lie in disruptive factors besides noise. Altered circadian rhythmicity may be one of the

factors contributing to sleep-wake abnormalities in the ICU. Previous investigators showed an absence of circadian rhythmicity varying between 20% and 80% of ICU patients. The patients who had rhythmicity showed large within-subject variability not normally demonstrated in healthy individuals. In contrast, we found all of our ICU patients to have present and robust circadian rhythms. However, recording core body temperature (CBT) as a marker for circadian rhythmicity showed shifted circadian phase positions (compared to the non-hospitalized control group), with an average displacement of 4.44 hours. The patient's APACHE III score was the only variable found to be significantly predictive of circadian displacement. These findings indicate that circadian rhythms are present, but altered in ICU patients, with the severity of illness being predictive of the circadian displacement. Although the relevance of circadian abnormalities for sleep in the ICU has yet to be confirmed in a direct study, our findings suggest that circadian displacement could (in part) be responsible for the previously demonstrated abnormal sleep-wake cycles in ICU patients.

Chapter 4 shows light-dark patterns in the ICU to be abnormal. The intensive care environment is often regarded as one of near-constant lighting, although there is little objective data on light levels in the ICU. The issue is important, as light is a synchronizer of the suprachiasmatic nuclei in the hypothalamus (the circadian pacemaker), where the body's circadian rhythms are orchestrated. Our CBT study demonstrated that ICU patients have abnormal circadian rhythms. To investigate if ICU light patterns could underlie these circadian rhythm disturbances, we studied patients' light exposure in two different hospitals and in healthy non-hospitalized controls. In comparison to controls, ICU patients were exposed to lower light levels during the day and higher light levels during the night. Although significant day–night variations in ICU light levels were present, the amplitude of the day–night differences in light exposure was smaller in ICU patients than in the non-hospitalized controls. Interestingly, no differences in light exposure between windowed and non-windowed rooms were demonstrated. Therefore, having a windowed ICU does not per definition guarantee normal light-dark patterns.

Chapter 5 demonstrates the effect of overnight sedation on the sleep-wake cycle of ICU patients. Sleep deprivation and sleep fragmentation have been shown to: adversely affect respiratory muscle performance, elevate arterial blood pressure, elevate serum catecholamines, cause cardiac arrhythmias, progress cardiac failure, contribute to delirium and agitation, and unfavorably alter the immune function in ICU patients. The realization that altered sleep/wake patterns in ICU patients may have important implications for health care in the ICU has spurred several investigators to improve these patterns by sedating patients overnight. None of these studies used continuous polysomnography to precisely assess 24-hour sleep patterns, however, so conclusions that normal night/day sleep/wake cycles can be restored by overnight sedation are premature.

We evaluated the effect of overnight sedation on daytime sleep/wake behavior in ICU patients using a within-subject study design. Continuous polysomnography recordings were performed for 72 hours, with the first 24 hours of recording

considered as the baseline. The second and third 24-hour periods involved continuous sedative infusion during the night time hours. The results of the baseline period showed results similar to our first study (Chapter 2), with a mean total sleep time of 7.3 hours, of which 51% was during daytime. Patients did not sleep any less during the day after a night of overnight sedation. While overnight sedation may result in a behavioral state resembling nighttime sleep, it appears not to be a good strategy for restoring a normal night/day sleep/wake cycle in ICU patients, contrary to previous investigations.

Chapter 6 describes a study of the circadian rhythm of one of our ICU patients. ICU patients are likely to develop altered circadian rhythmicity. It has been suggested that this is caused by a lack of synchronization of the biological clock due to the absence of proper time cues in the ICU environment. For a period of 9 days, core body temperature (as a measure of circadian rhythmicity) and a modified mini-mental-state-exam where recorded in one of our ICU patients (female, 67 yrs), whose circadian rhythms were initially severely disrupted. The patient's only reliable source of time information was the television, tuned to the British Broadcasting Company (BBC). During the recording period, her circadian rhythms and mental capacity improved significantly. This case study suggests that normal circadian rhythms maybe restored in the ICU by a single effective time source, and indicates that improvement of circadian rhythmicity may be associated with positive clinical outcome.

WORDS OF GRATITUDE.

Being a "Groninger", I will keep this part of the chapter short, since many people abuse it to excuse themselves for their behavior while suffering through the ordeal of their PhD project. I did not suffer, nor did any of my friends or family. There are several people however, who have been directly and indirectly involved with this dissertation and should receive the credit they deserve.

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Beauty,
I Love You.

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